PDR for Nonprescription Drugs® and Dietary Supplements™ entry for **Triaminic Vapor Patch-Menthol Scent** (Novartis Consumer)

Description

Drug Facts

Active ingredients (in each patch)

Camphor 4.7% ..... Cough suppressant

Menthol 2.6% ..... Cough suppressant

(*back to top*)

Uses temporarily relieves these symptoms:

· cough due to a cold · cough due to minor throat and bronchial irritation · cough to help you sleep

(*back to top*)

Warnings

For external use only

Flammable: Keep away from fire or flame

Do not use

· near an open flame · by adding to hot water · in a microwave oven · in

a container in which water is being heated

Ask a doctor before use if the child has

· cough that occurs with too much phlegm (mucus) · a persistent or chronic cough such as occurs with asthma

When using this product

· do not use more than directed · do not take by mouth or place in nostrils · do not apply to eyes, wounds, or damaged skin

Stop use and ask a doctor if

· a cough persists for more than 7 days, comes back, or occurs with fever, rash, or persistent headache. These could be signs of a serious condition · too much skin irritation occurs or gets worse

Keep out of reach of children. If swallowed, get medical help or contact a poison control center right away.

(*back to top*)

Dosage and Administration

Children 2 to under 12 years of age:

· Remove plastic backing · Apply to the throat or chest · Clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth · More than one patch may be used · Applications may be repeated up to three times daily or as directed by a doctor · May use with other cough suppressant products

Children under 2 years of age: Ask a doctor

Other Information:

· store at controlled room temperature 20-25°C (68-77°F) · protect from excessive heat

(*back to top*)

Inactive Ingredients

TRIAMINIC® Vapor Patch

-Mentholated Cherry Scent Cough Suppressant

acrylic ester copolymer, aloe vera gel, eucalyptus oil, glycerin, karaya, propylene glycol, purified water, wild cherry fragrance

TRIAMINIC® Vapor Patch

-Menthol Scent Cough Suppressant

acrylic ester, copolymer, aloe vera gel, eucalyptus oil, glycerin, karaya, purified water, spirits of turpentine

(*back to top*)

How Supplied: Packet of 6 patches, ointment on a breathable cloth patch.

Questions: call **1-800-452-0051**

For more information about Triaminic® visit our website at www.triaminic.com

NOVARTIS

Novartis Consumer Health, Inc.,

Summit, NJ 07901-1312 ©2001

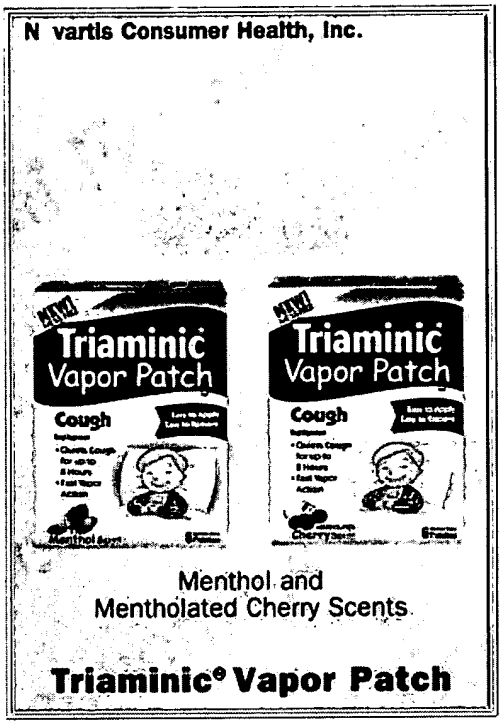
(*back to top*)

PRODUCT PHOTO(S):

NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the

manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.



Stedman's Definition

Enter a word or phrase to search for. (HINT: Highlight a word with the mouse and use copy and paste)

PDR for Nonprescription Drugs® and Dietary Supplements™ entry for **BenGay External Analgesic Products** (Pfizer Inc., Warner-Lambert Healthcare)

Description

Description: BENGAY products contain menthol in an alcohol base gel, combinations of methyl salicylate and menthol in cream and ointment bases, as well as a combination of methyl salicylate, menthol and camphor in a non-greasy cream base; all suitable for topical application.

In addition to the Original Formula Pain Relieving Ointment (methyl salicylate, 18.3%; menthol, 16%), BENGAY is offered as BENGAY Greaseless Pain Relieving Cream (methyl salicylate, 15%; menthol, 10%), an Arthritis Formula NonGreasy Pain Relieving Cream (methyl salicylate, 30%; menthol, 8%), an Ultra Strength NonGreasy Pain Relieving Cream (methyl salicylate 30%; menthol 10%; camphor 4%), Vanishing Scent NonGreasy Pain Relieving Gel (2.5% menthol), and S.P.A. (Site Penetrating Action) Pain Relieving Cream (10% menthol) with a fresh scent.

(*back to top*)

Action and Uses: Methyl salicylate, menthol and camphor are external analgesics which stimulate sensory receptors of warmth and/or cold. This produces a counter-irritant response which provides temporary relief of minor aches and pains of muscles and joints associated with simple backache, arthritis, strains and sprains.

Several double-blind clinical studies of BENGAY products containing menthol-methyl salicylate have shown the effectiveness of this

combination in counteracting minor pain of skeletal muscle stress and arthritis.

Three studies involving a total of 102 normal subjects in which muscle soreness was experimentally induced showed statistically significant beneficial results from use of the active product vs. placebo for lowered Muscle Action Potential (spasms), greater rise in threshold of muscular pain and greater reduction in perceived muscular pain.

Six clinical studies of a total of 207 subjects suffering from minor pain due to osteoarthritis and rheumatoid arthritis showed the active product to give statistically significant beneficial results vs. placebo for greater relief of perceived pain, increased range of motion of the affected joints and increased digital dexterity. In two studies designed to measure the effect of topically applied BENGAY vs. placebo on muscular endurance, discomfort, onset of exercise pain and fatigue, 30 subjects performed a submaximal three-hour run and another 30 subjects performed a maximal treadmill run. BENGAY was found to significantly decrease the discomfort during the submaximal and maximal runs, and increase the time before onset of fatigue during the maximal run.

Applied before workouts, BENGAY relaxes tight muscles and increases circulation to make exercising more comfortable, longer.

To help reduce muscle ache and soreness after exercise, BENGAY can be applied and allowed to work before taking a shower.

(*back to top*)

Directions: Apply generously and gently massage into painful area until BENGAY disappears. Repeat 3 to 4 times daily.

(*back to top*)

Warnings: For external use only. Do not use with a heating pad. Keep away from children to avoid accidental poisoning. Do not bandage tightly. Do not swallow. If swallowed, induce vomiting and call a physician. Keep away from eyes, mucous membranes, broken or irritated skin. If skin redness or irritation develops, pain lasts for more than 10 days, or with arthritis--like conditions in children under 12, do not use and call a physician.

(*back to top*)

PRODUCT PHOTO(S):

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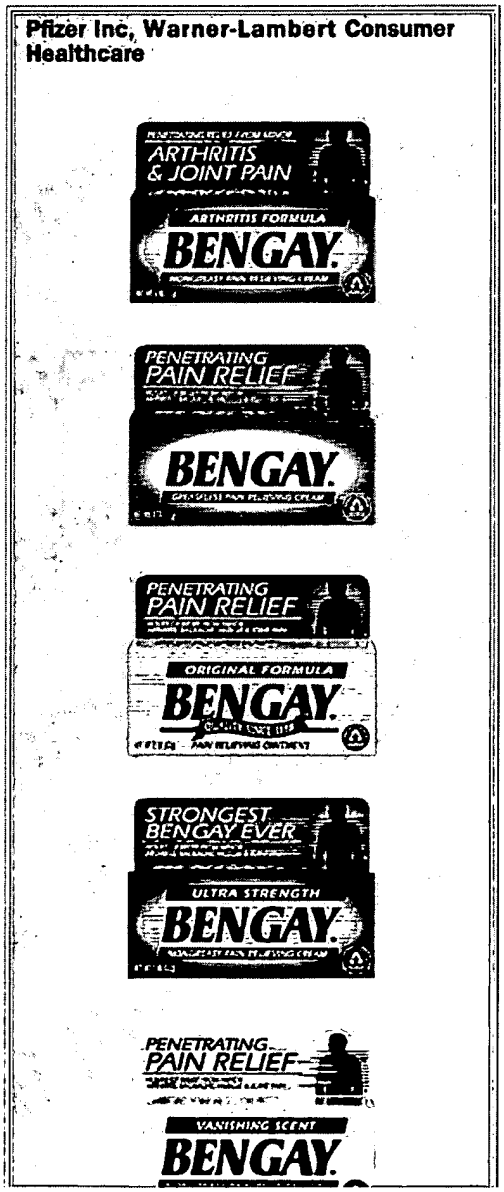
The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.

Pfizer Inc, Warner-Lambert Consumer Healthcare



Stedman's Definition

Enter a word or phrase to search for. (HINT: Highlight a word with the mouse and use copy and paste)

PDR for Nonprescription Drugs® and Dietary Supplements™ entry for **Vicks VapoRub Ointment** (Procter & Gamble)

Indications and Usage

Uses:

On chest & throat temporarily relieves:

cough
- nasal congestion [due to the common cold]

On aching muscles temporarily relieves:

- minor aches & pains

(*back to top*)

Active Ingredients: **Purpose:**
Camphor 5.2% ..... Cough suppressant, nasal decongestant & topical analgesic
Eucalyptus oil 1.2% ..... Cough suppressant & nasal decongestant
Menthol 2.8% ..... Cough suppressant, nasal decongestant & topical analgesic

Inactive Ingredients: Carbomer 954, Cedarleaf Oil, Cetyl Alcohol,

Cetyl Palmitate, Cyclomethicone Copolyol, Dimethicone Copolyol, Dimethicone, EDTA, Glycerin, Imidazolidinyl Urea, Isopropyl Palmitate, Methylparaben, Nutmeg Oil, Peg-100 Stearate, Propylparaben, Purified Water, Sodium Hydroxide, Stearic Acid, Stearyl Alcohol, Thymol, Titanium Dioxide, Turpentine Oil.

(*back to top*)

Directions:

see important warnings under " When using this product "

- under 2 yrs. ask a doctor
- adults and children 2 yrs. & older: Rub a thick layer on chest & throat or rub on sore aching muscles. If desired, cover with a soft cloth but keep clothing loose. Repeat up to three times daily.

(*back to top*)

Warnings:

F r external use only; avoid contact with eyes.

Do not use:

- by mouth
- with tight bandages
- in nostrils
- on wounds or damaged skin

Ask a doctor before use if you have:

- excessive phlegm (mucus)
- asthma
- emphysema
  persistent or chronic cough
- cough associated with smoking

When using this product do not:

- **heat**

- **micr wave**
- **use near an open flame**
- **add to hot water r any container where heating water. May cause splattering and result in burns.**

Stop use and ask a doctor if:

- muscle aches/pains persist more than 7 days or come back
- cough lasts more than 7 days, comes back, or occurs with fever, rash, or headache that lasts.

These could be signs of a serious condition.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of accidental ingestion, get medical help or contact a Poison Control Center right away.

Other Information:

Store at room temperature

(*back to top*)

How Supplied: (ointment) Available in 1.5 OZ (40 g), 3.0 OZ (90 g) and 6.0 OZ (170 g) plastic jars. **(cream)** 2.0 OZ (56 g) tube.

Questions? 1 800 358-8707

DB Name	Query	Hit Count	Set Name
USPT,PGPB	l24 and l18	15	L25
USPT,PGPB	l23 and l20	57	L24
USPT,PGPB	l22 and l17	388	L23
USPT,PGPB	ethylene glycol or propylene glycol or dipropylene glycol or butylene glycol or hexylene glycol or polyethylene glycol or glycerin or sorbitol or panthenol or urea or alkoxylated glucose or hexanetriol or glucose ethers or sodium hyaluronate or soluble chitosan or glycerin	229815	L22
USPT,PGPB	l19 and l20	1	L21
USPT,PGPB	patch or plaster	46402	L20
USPT,PGPB	l18 and l17 and l16	14	L19
USPT,PGPB	essential oil	5365	L18
USPT,PGPB	menthol with active	552	L17
USPT,PGPB	l15 and l13	664	L16
USPT,PGPB	menthol	4731	L15
USPT,PGPB	l13 and l10	9	L14
USPT,PGPB	polyhydric alcohol	28750	L13
USPT,PGPB	l10 and l11	0	L12
USPT,PGPB	mentholatum	7	L11
USPT,PGPB	l9 and l5 and l4	66	L10
USPT,PGPB	l7 or l8	65535	L9
USPT,PGPB	essence.bi.	61039	L8
USPT,PGPB	essential oil.bi.	5243	L7
USPT,PGPB	ointment.bi.	23122	L6
USPT,PGPB	patch.bi.	34105	L5
USPT,PGPB	menthol.bi.	4715	L4
USPT,PGPB	4136163.pn.	1	L3
USPT,PGPB	4157384.pn.	1	L2
USPT,PGPB	5700478.pn.	1	L1

WEST

Freeform Search

Database:
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- JPO Abstracts Database
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- Derwent World Patents Index
- IBM Technical Disclosure Bulletins

Term: 124 and 118

Display: 10 **Documents in Display Format:** CIT **Starting with Number** 1

Generate: ○ **Hit List** ◉ **Hit Count** ○ **Image**

Search | Clear | Help | Logout | Interrupt

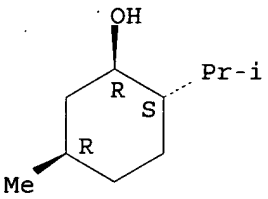
Main Menu | Show S Numbers | Edit S Numbers | Preferences

Search History

Today's Date: 10/22/2001

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 2216-51-5 REGISTRY
CN Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1R,2S,5R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclohexanol, 5-methyl-2-(1-methylethyl)-, [1R-(1.alpha.,2.beta.,5.alpha.)]-
CN Menthol, (1R,3R,4S)-(-)- (8CI)
OTHER NAMES:
CN (-)-(1R,2S,5R)-Menthol
CN (-)-Menthol
CN (-)-Menthyl alcohol
CN (-)-trans-p-Methan-cis-3-ol
CN (1R)-(-)-Menthol
CN (R)-(-)-Menthol
CN 1R-Menthol
CN D-(-)-Menthol
CN l-(-)-Menthol
CN **l-Menthol**
CN Levomenthol
FS STEREOSEARCH
DR 98167-53-4
MF C10 H20 O
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
CA, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DETHERM*, DIOGENES, DIPPR*, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MSDS-OHS, NAPRALERT, PROMT, RTECS*, SPECINFO, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2278 REFERENCES IN FILE CA (1967 TO DATE)
34 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2284 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> FIL MEDLINE, BIOSIS, CA, CAPLUS, CAOLD, EMBASE, USPATFULL, PROMT
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	5.92	6.37

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=> s l1 or menthol
   6 FILES SEARCHED...
L2        25417 L1 OR MENTHOL

=> s pain patch
L3           38 PAIN PATCH

=> s ointment
L4        44403 OINTMENT

=> s patch
L5       182922 PATCH

=> s essential oil
L6        40269 ESSENTIAL OIL

=> d his

     (FILE 'HOME' ENTERED AT 10:03:39 ON 22 OCT 2001)

     FILE 'REGISTRY' ENTERED AT 10:05:26 ON 22 OCT 2001
L1             1 S L-MENTHOL/CN

     FILE 'MEDLINE, BIOSIS, CA, CAPLUS, CAOLD, EMBASE, USPATFULL, PROMT'
     ENTERED AT 10:06:26 ON 22 OCT 2001
L2         25417 S L1 OR MENTHOL
L3            38 S PAIN PATCH
L4         44403 S OINTMENT
L5        182922 S PATCH
L6         40269 S ESSENTIAL OIL

=> s l2 and l4 and l5 and l6
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L7          10 L2 AND L4 AND L5 AND L6

=> dup rem
ENTER L# LIST OR (END):l7
DUPLICATE IS NOT AVAILABLE IN 'CAOLD'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L7
L8            9 DUP REM L7 (1 DUPLICATE REMOVED)

=> d l8 1-9 bib, ab, kwic

L8   ANSWER 1 OF 9  CA  COPYRIGHT 2001 ACS                DUPLICATE 1
AN   135:51093  CA
TI   Drugs for relieving hemicrania
IN   Yokoyama, Hideakira; Hamamoto, Hidetoshi
PA   Teikoku Seiyaku Co., Ltd., Japan; Rohto Pharmaceutical Co., Ltd.
SO   PCT Int. Appl., 17 pp.
     CODEN: PIXXD2
DT   Patent
LA   Japanese
FAN.CNT 1
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
PI   WO 2001043736      A1   20010621       WO 1999-JP7008   19991214
         W:  AU, CA, JP, US
         RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE
AB   Drugs having an effect of relieving hemicrania contain l-menthol
     and an essential oil exclusively as the active
     ingredients.  More particularly, ointments and patches having an effect
of
     relieving hemicrania to be topically administered for relieving
     hemicrania, are prepd. by blending l-menthol and an
     essential oil with ointment compns. contg. a
     water-sol. polymer, a polyhydric alc. and water.  An ointment
     contained polyacrylic acid 1, Na polyacrylate 5, Na CMC 5, gelatins 0.4,
     polyvinyl alc. 0.2, tartaric acid 0.2, Na edetate 0.1, glycerin 22,
     Al(OH)3 0.3, Polysorbate 80 0.1, castor oil 0.5, methylparaben 0.1, l-
     menthol 0.3, peppermint oil 0.2, and distd. water q.s. to 100 %.
RE.CNT  11
RE
(1) Edward, R; US 5629281 A 1997 CA
(2) Goebel; Front Headache Res, (Experimental Headache Models) 1995, V5, P331
    CA
(3) Goebel; Phytomedicine 1995, V2(2), P93 CA
(5) Intreprinderea de Antibiotice; RO 66574 B 1980 CA
(6) Konno, T; JP 58225012 A 1983 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB   Drugs having an effect of relieving hemicrania contain l-menthol
     and an essential oil exclusively as the active
     ingredients.  More particularly, ointments and patches having an effect
of
     relieving hemicrania to be topically administered for relieving
     hemicrania, are prepd. by blending l-menthol and an
     essential oil with ointment compns. contg. a
     water-sol. polymer, a polyhydric alc. and water.  An ointment
     contained polyacrylic acid 1, Na polyacrylate 5, Na CMC 5, gelatins 0.4,
     polyvinyl alc. 0.2, tartaric acid 0.2, Na edetate 0.1, glycerin 22,
     Al(OH)3 0.3, Polysorbate 80 0.1, castor oil 0.5, methylparaben 0.1, l-
     menthol 0.3, peppermint oil 0.2, and distd. water q.s. to 100 %.
```

ST hemicrania treatment **ointment menthol**
essential oil; **patch** hemicrania treatment
menthol essential oil; peppermint oil
menthol ointment migraine treatment

IT Essential oils
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(juniper; topical prepns. contg. **menthol** and essential oils for relieving hemicrania)

IT Essential oils
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lavender; topical prepns. contg. **menthol** and essential oils for relieving hemicrania)

IT Headache
(migraine; topical prepns. contg. **menthol** and essential oils for relieving hemicrania)

IT Drug delivery systems
(ointments; topical prepns. contg. **menthol** and essential oils for relieving hemicrania)

IT Essential oils
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peppermint; topical prepns. contg. **menthol** and essential oils for relieving hemicrania)

IT Alcohols, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyhydric; topical prepns. contg. **menthol** and essential oils for relieving hemicrania)

IT Essential oils
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rose; topical prepns. contg. **menthol** and essential oils for relieving hemicrania)

IT Essential oils
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rosemary; topical prepns. contg. **menthol** and essential oils for relieving hemicrania)

IT Drug delivery systems
(tapes; topical prepns. contg. **menthol** and essential oils for relieving hemicrania)

IT Essential oils
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(topical prepns. contg. **menthol** and essential oils for relieving hemicrania)

IT **2216-51-5**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(topical prepns. contg. **menthol** and essential oils for relieving hemicrania)

IT 9002-89-5, Polyvinyl alcohol 9003-01-4, Polyacrylic acid 9003-04-7, Sodium polyacrylate 9004-32-4, Sodium CMC
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(topical prepns. contg. **menthol** and essential oils for relieving hemicrania)

L8 ANSWER 2 OF 9 PROMT COPYRIGHT 2001 Gale Group

AN 1999:393652 PROMT
TI Body care: Getting better all the time.
SO European Cosmetic Markets, (June 1999) Vol. 16, No. 6, pp. 231(1).
ISSN: 0957-1515.
PB Wilmington Publishing Ltd.
DT Newsletter
LA English
WC 11040
FULL TEXT IS AVAILABLE IN THE ALL FORMAT
AB MARKET SUMMARY: Overall the body care market fared well across the Big 5
European markets and due to generally low penetration of these products, the sector's potential looks promising. Key NPD trends include the introduction of niche items which encourage consumers to trade up. The depilatories market is continuing to make significant gains.

Subscription: 695 British pound sterling per year as of 1/97. Published monthly. Contact Wilmington Publishing, Wilmington House, Church Road, Dartford, Kent UA2 7EF. Phone 44-1322-277788. Fax 44-1322-276476.
TX Jeanne Piaubert (Groupe Bogart) launched two new products in March, Onguent Peau d'Ange ("Angel's Skin **Ointment**") and Certitude Minceur. Peau d'Ange hydrates the skin and nourishes and protects it. Its formula includes NMF, glycerine, shea butter,. . .
In . . . fight. cellulite-related skin problems; Body Exfoliating Lipogel incorporates sea salt, jojoba oil and soya lecithin as well as a fine **essential oil** selection of geranium, lavender, rosemary, lemon and sweet orange oils; Wellness Body Contouring Bath contains algae extract, sea salt and. . .
In . . . added three new body care products to its Ultima H range. Ultima H Extraordinaire Stretch Mark Creme and Body Repair **Patch** improve the skin's elasticity and provide intensive hydration to the appropriate area and Ultima II Revitalising Gel for legs and. . .
In . . . bust area. Also in the summer Givenchy (LVMH) unveiled Swisscare Leg Shaper, a firming relaxing shaping gel. The formula includes **menthol** and liquorice to refresh, ginkgo biloba and horse chestnut to eliminate toxins and reduce water retention, ginseng and natural soya. . .

L8 ANSWER 3 OF 9 USPATFULL
AN 1998:19724 USPATFULL
TI Method and therapeutic system for smoking cessation
IN Baker, Richard W., Palo Alto, CA, United States
Santus, Giancarlo, Milan, Italy
Vintilla-Friedman, Susan, Cupertino, CA, United States
PA Pharmacia & Upjohn AB, Sweden (non-U.S. corporation)
PI US 5721257 19980224
AI US 1995-484987 19950607 (8)
RLI Continuation of Ser. No. US 1994-221914, filed on 31 Mar 1994, now patented, Pat. No. US 5593684 which is a continuation of Ser. No. US 1993-103262, filed on 4 Aug 1993, now patented, Pat. No. US 5362496
DT Utility
FS Granted
EXNAM Primary Examiner: Criares, Theodore J.
LREP Pravel, Hewitt, Kimball & Krieger
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN 14 Drawing Figure(s); 12 Drawing Page(s)

LN.CNT 2100
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for treating conditions responsive to nicotine therapy, and particularly for smoking cessation therapy and for reducing nicotine craving, is described that utilizes transdermal nicotine delivery for obtaining base-line nicotine plasma levels coupled with transmucosal administration of nicotine to satisfy transient craving.
SUMM . . . Studies using human cadaver skin in vitro are likewise consistent with this finding. Typical permeabilities during the first day of **patch** use are on the order of 0.1 mg/cm.sup.2 .multidot.h, increasing to 0.4 mg/cm.sup.2 .multidot.h and more at later times. Systemic. . .
SUMM . . . 1:7-10 reported on the results of a double-blind study in which they determined that long-term use of a transdermal nicotine **patch** significantly increased the quit rate in cigarette smokers. The results of this study showed that the number of abstainers in. . . group. In another study reported by Mulligan et al. (1990) Clin. Pharmacol. Ther. 47:331-337, the use of a transdermal nicotine **patch** in a 6-week placebo-controlled double-blind study resulted in a significant degree of smoking cessation. Finally, a report by Rose et. . .
SUMM . . . skin-distal side, the depot layer containing a sufficient quantity of nicotine to maintain a useful flux of nicotine from the **patch** for a total time period of 12 hours or more;
SUMM According to other embodiments, the **patch** may take the form of a reservoir system, in which the depot of nicotine is separated from the skin by a nonporous polymeric membrane, through which the nicotine diffuses at a controlled rate. The **patch** may also be in the form of a monolithic matrix, consisting of a single phase solution or mixture of nicotine. . .
DRWD FIG. 6 is a graph of nicotine delivery (mg/cm.sup.2) through 100-micron thick Elvax 880 membranes, from a **patch** containing 200 mu L pure nicotine, with a membrane area of 4.5 cm.sup.2, as a function of time (hr).
DRWD FIG. 7 is a graph of nicotine delivery (mg/cm.sup.2) through 100-micron thick Elvax 88 membranes, from a **patch** containing 200 mu L of a 5% suspension of nicotine in a 20 wt % sodium sulfate solution, with a. . .
DRWD . . . patches with nylon or polyethylene membranes, as a function of time (hr). The nicotine content is 20-25 mg, and the **patch** area is 3.9 cm.sup.2.
DRWD . . . the present invention delivering either 22 mg (.quadrature.) or 27 mg (.largecircle.) of nicotine or the PROSTEP 22 mg (.box-solid.) **patch** as a function of time (hr) .
DETD "**Essential oil**" refers to a natural oil with a distinctive scent secreted by the glands of certain aromatic plants having terpenes as. . .
DETD . . . nicotine system described in the present invention is shown in FIG. 2. Referring now to this figure, the nicotine dispensing **patch**, 1, comprises an impermeable backing layer, 2, and a monolithic matrix layer, 3, which both serves as a depot for. . .
DETD The impermeable backing layer, 2, defines the non-skin facing, or skin distal, side of the **patch** in use. The functions of the backing layer are to provide an occlusive layer that prevents loss of nicotine to the environment, and to protect the **patch**. The material chosen should therefore be nicotine resistant, and should exhibit

minimal nicotine permeability. The backing layer should be opaque,. .
.

DETD . . . in theory patches of this type with a bigger load can be made. Also, the amount of nicotine in the **patch** as made may exceed the delivered load because, as the **patch** becomes exhausted, there will be an insufficient concentration gradient to remove all the nicotine. Consequently, the activity of the **patch** may fall below useful levels.

DETD . . . elimination of skin irritation. The release mechanism for the nicotine is diffusion under a concentration gradient. Therefore, even if the **patch** were to be ingested, the nicotine release would be still a gradual process, and the victim would not be exposed. . .

DETD To ensure that a user cannot be exposed to a toxic dose when the **patch** is used correctly, the in vitro nicotine flux from the **patch** must stay within certain limits. This is a much more critical issue with nicotine than with most drugs, because nicotine. . . 20-fold or more between individuals and between different skin sites on the same individual. It is thus clear that a **patch** with a large nicotine load must be able to control release of that load, such that the in vitro flux from the **patch** does not exceed about 10 times, preferably about 5 times, and more preferably about equals, the average skin permeation rate. Of course, embodiments where the in vitro flux from the **patch** is less than the skin permeation rate, such that the systemic absorption is controlled primarily by the **patch** rather than the skin, are acceptable, so long as the systemic nicotine level can be sustained above the necessary minimum.

.
.

DETD . . . by means of a porous or nonporous overlay coated wholly or partly with adhesive, by an adhesive layer between the **patch** and skin, or by an annulus of adhesive around the periphery of the **patch**. Of course, the mixed reservoir/monolith embodiments with adhesive medical tapes do not require additional adhesive.

DETD If an adhesive layer is to be included as an integral part of the **patch**, the adhesive should be nicotine compatible and permit a useful nicotine flux. In addition, the adhesive should satisfy the general. . .

DETD Loss of nicotine from the **patch** after manufacture should be kept to a minimum. Normally, the skin-facing side of the **patch** will be covered with a peel strip until the **patch** is used. As stressed throughout, nicotine is volatile, and retention of the nicotine load within the **patch** during storage requires that the outer **patch** layers be extremely nicotine-resistant and nicotine-impermeable. The peel strip therefore should possess the same properties as the backing layer, and. . .

DETD According to a particularly preferred embodiment, the transdermal nicotine **patch** will comprise a rounded-rectangular, "skin tone" colored **patch** on a clear, rectangular release liner. More specifically, the **patch** will comprise a flexible, occlusive film backing, a multilaminate matrix containing nicotine, a skin adhesive layer, and a protective release. . .

DETD Another embodiment of the invention is shown in FIG. 3. Referring now to this figure, the nicotine dispensing **patch**, 4, comprises an impermeable backing layer, 2, a nicotine reservoir, 5, and a polymer membrane, 6. The backing layer may. . .

DETD . . . layer. The reservoir layer does not contribute to any measurable extent to the rate-controlling mechanism. To discourage

tampering with the **patch**, or misuse of the contents, it may be desirable to mix the nicotine with other materials as described in U.S..

. .

DETD If the **patch** is to be loaded with a comparatively small quantity of nicotine, then the nicotine can be conveniently kept in contact. . . can be used. The disk also decreases the user's risk of exposure to a high dose of nicotine should the **patch** become accidentally ruptured.

DETD The polymer membrane layer, 6, is the rate-controlling means that regulates the flux of nicotine from the **patch** to the skin. The criteria for selection of a suitable material are those discussed in the background section above, namely. . . should also be compatible with the other components, and workable by standard techniques that are used in fabrication of the **patch**, such as casting or heat sealing.

DETD Dense nonporous membranes have a substantial advantage over microporous materials. Microporous membranes release the contents of the **patch** by pore flow. Thus, in areas of the pores, the skin is exposed to raw nicotine. Also, in the case. . . so that the system is quickly exhausted, and the skin is flooded with excess nicotine for the life of the **patch**. In contrast, diffusion of nicotine through a nonporous film takes place by dissolution of the nicotine in the film, followed. . .

DETD Alternatively, it may be possible to purchase the membrane already in film form. This type of transdermal **patch** may be prepared by heat-sealing the backing to the membrane layer around the perimeter of the **patch**. The nicotine formulation may be added either before or after heat sealing. If the formulation is added before heat sealing,.

. .

DETD . . . the reservoir side of the membrane, the nicotine flux through the membrane remains relatively constant over the life of the **patch**.

DETD . . . discussed above, these kinds of considerations matter more when dispensing nicotine than with many other substances. Suppose that a transdermal **patch**, tested in vitro, delivers a substantial fraction of its total drug load during the first few hours, at a flux. . . The in vitro flux then falls off to levels that are well below the average skin permeation rate until the **patch** is exhausted. When this **patch** is applied to the user, the skin will be saturated with drug and the drug will pass through the skin. . .

DETD . . . depot" phenomenon may be perfectly acceptable, or even preferable, since it tends to balance out the falling flux from the **patch**.

DETD . . . patches currently available exhibit this effect and function satisfactorily in this way. However, for nicotine, the situation is different. A **patch** that can avoid this high initial drug burst, with consequent skin irritation or risk of overdose, is desirable. Any initial flux from the **patch** should not exceed a maximum of 2 mg/cm.sup.2 h, and more preferably should not exceed 1 mg/cm.sup.2 .multidot.h. Any flux. . . of the patient, and the drug flux required, it may be easier to stay within this limit with a reservoir-type **patch**. The risk of accidental overdose if the **patch** is damaged or ingested, however, is minimized with monolithic embodiments. There will therefore be circumstances where one

or the other type of **patch** is preferably indicated.

DETD . . . in FIG. 4 exploits the advantages of both reservoir and monolith systems. Referring now to this figure, the nicotine dispensing **patch**, 7, comprises an impermeable backing layer, 2, a monolithic matrix layer, 3, and a polymer membrane layer, 8. The backing. . .

DETD . . . than the monolith material, so that the adhesive layer serves as a thin membrane limiting flux of nicotine from the **patch**.

DETD . . . from 3M Company. The additional resistance to permeation created by the tape assists in holding the nicotine load in the **patch** and moderates the initial high drug flux.

DETD . . . an overdose of nicotine is reduced, because the monolith cannot release its nicotine load in a single burst if the **patch** is damaged or even swallowed.

DETD . . . and 4,920,989, each of which is expressly incorporated herein by reference. More specifically, according to one embodiment, a transdermal nicotine **patch** similar to the PROSTEP.SM. will be employed. This **patch** comprises, proceeding from the visible outer surface toward the inner surface attached to the skin, (1) a foam tape and. . .

DETD Alternatively, a nicotine **patch** similar to the Habitrol.SM. **patch** can be used. This **patch** comprises, proceeding from the visible outer surface toward the inner surface attached to the skin, (1) an aluminized-backing film; (2). . .

DETD Other embodiments will employ a nicotine **patch** similar to the Nicoderm.RTM. nicotine transdermal system, available from ALZA Corporation, Palo Alto, Calif. This **patch** is a multilayered rectangular film containing nicotine as the active agent. Proceeding from the visible surface toward the surface attached. . .

DETD E. **Patch** Specifications

DETD The transdermal nicotine **patch** provides a base line or steady state nicotine level to the patient. The total amount of nicotine released by the **patch** during the period of use will vary depending on the user's body size, history of exposure to nicotine, and response. . .

DETD General guidelines for **patch** design must ensure that the patient is protected at all times from toxic doses of nicotine, and must also ensure. . . receives a dose of nicotine that will be effective for smoking cessation therapy. The in vitro flux from any individual **patch** used for the intended therapy should remain below about 800 mu g/cm.sup.2 .multidot.h, preferably below 600 mu g/cm.sup.2 .multidot.h, and more preferably below 400 mu g/cm.sup.2 .multidot.h during the life of the **patch**. Staying within these limits ensures that a patient with unusually permeable skin can never receive a toxic dose.

DETD The size of the **patch** will vary according to the amount of nicotine to be delivered. To deliver 25 mg in a 24-hour period, the **patch** would have a skin-contacting area of about 15-30 cm.sup.2. To maximize patient acceptance and compliance, and to minimize any skin irritation, the **patch** size should not exceed about 45 cm.sup.2 maximum skin covering area. With the systems and release characteristics taught by applicant, it should be possible to keep the **patch** size in the range 1-50 cm.sup.2, preferably 20-35 cm.sup.2.

DETD . . . reduces immediate metabolism by the liver and intestinal wall flora. Oral drug dosage forms (e.g., lozenge, capsule, gum, tablet, suppository, **ointment**, gel, pessary, membrane, and powder) are

typically held in contact with the mucosal membrane and disintegrate and/or dissolve rapidly to. . .

DETD . . . vanilla, and the like; essential oils such as peppermint, spearmint and the like; or other flavor, such as aniseed, eucalyptus, 1-**menthol**, carvone, anethole and the like, to mask the taste of nicotine. See Hall et al. Food Technol. 14:488 (1960); 15:20. . .

DETD . . . the production of inclusion complexes of both the nicotine and the flavorant. This embodiment is employed, for example, when an **essential oil**, or other volatile flavorant, such as carvone or **menthol**, is used in the lozenge formulation. As in the case of the nicotine inclusion complexes described herein, incorporation of the. . .

DETD Whereas the **patch** serves to provide a base line or steady state nicotine level, the transmucosal administration of nicotine provides periodic transient blood. . .

DETD . . . base line level of nicotine plasma level. The present invention fulfills this objective through the use of a transdermal nicotine **patch** in combination with the transmucosal administration of nicotine, and preferably the administration of nicotine through the oral mucosa, and most preferably, with nicotine lozenges. The transdermal **patch** and the transmucosal administration of nicotine operate in a complimentary manner with the transdermal **patch** providing the steady-state systemic levels of nicotine in the bloodstream to which the smoker has become accustomed, whereas the transmucosal. . .

DETD . . . for an individualized approach to smoking cessation therapy. Specifically, the total amount of nicotine delivered, the delivery mode, i.e., via **patch** or transmucosal delivery method and regimen, i.e., the order of administration and duration of use of either the **patch** and/or the transmucosal delivery formulation, can be varied to take into account the patient's needs, e.g., the therapeutic indication, the. . .

DETD For example, according to one embodiment, the transdermal **patch** and transmucosal administration of nicotine are first used concurrently and simultaneously for a period of from about 3 to 12. . . preferably from about 4 to 8 weeks, and most preferably from about 4 to 6 weeks, in which only the **patch** or only the transmucosal nicotine formulation is used.

DETD Other embodiments will employ different dosage levels of either the **patch** and/or the transmucosal nicotine formulation to suit the needs of those patients with either a relatively high or low nicotine. . . more on the Fagerstrom test, will typically consist of three phases. During the initial phase, a high dosage nicotine transdermal **patch**, typically, with a high loading of nicotine in the range of about 30-60 mg, and preferably, about 40-45 mg, is. . . from about 4 to 8 weeks. Typically, transmucosal administration of nicotine will be used in conjunction with this high dosage **patch**. Subsequently, a transdermal **patch** with a lower loading of nicotine, typically in the range of about 10-30 mg, and preferably, about 20-25 mg, and. . . of from about 4 to 8 weeks. Finally, for a period of from about 4 to 6 weeks, either the **patch** or the transmucosal administration of nicotine may be used alone.

DETD . . . moderate smoker, i.e., those scoring 6 or less on the Fagerstrom test. For example, during the initial phase, a transdermal **patch** with a moderate loading of nicotine, typically in the range of about 10-40 mg, and preferably, about 25-30 mg, is. . . administration of nicotine. The second phase of this smoking cessation program will consist of administration of a lower dosage transdermal **patch**, typically containing nicotine in the range of about 10-30 mg, and preferably, about 20-25 mg, optionally, with the transmucosal administration. . . used for a period of from about 4 to 8 weeks. During the final phase or weaning period, either the **patch** or transmucosal administration will be used alone.

DETD . . . cessation program for the light smoker can be developed using the compositions and methods described herein. For example, a transdermal **patch** containing a relatively low loading of nicotine, typically containing nicotine in the range of about 10-30 mg, and preferably, about. . . used for a period of from about 4 to 8 weeks. During the final phase or weaning period, either the **patch** or the transmucosal formulation will be used alone.

DETD . . . cigarette smoking. Thus, and with many patients, it is possible to reduce the incidence of smoking with either the transdermal **patch** or the transmucosal formulation alone.

DETD TABLE III

Property	Low Dosage **Patch**	High Dosage **Patch**
Dosage Strength	22 mg/20 cm.sup.2	27 mg/20 cm.sup.2
Size (cm.sup.2)	20	20
Nicotine content (mg)	31.4	37.7
24 Hour Delivery (mg).sup.2	22	27
Flux (mg/cm.sup.2 /24 hour).sup.3	1.1	1.35
Total Nicotine Delivered (%)	73	75
Patch Weight (mg)	837	843
Thickness (microns)	333	344

.sup.2 Based on residual content from in vivo performance.

.sup.3 Estimated from in. . .

DETD TABLE IV

Composition	Nicotine **Patch** A	Nicotine **Patch** B
Dosage	22 mg/20 cm.sup.2	27 mg/20 cm.sup.2
Nicotine content (mg)	31.4	37.7
Acrylic adhesive matrix (mg)	70.2	70.2
Butylated hydroxytoluene (mg)	0.6	0.6

Polyester. . .

DETD The **patch**-making procedure and release tests described in Example 9 were repeated using the same membrane, but with a load of 200.

. .

DETD The **patch**-making procedure and release tests described in Example 11 were repeated with a 22- mu m thick film of Sclairfilm HD-2-PA as the membrane. The flux from the **patch** remained roughly constant at about 80 mu g/cm.sup.2 .multidot.h for the first 60 hours, falling to about 30 mu g/cm.sup.2. . .

DETD The **patch**-making procedure and release tests described in Example 11 were repeated with a 50- mu m thick film of Sclairfilm HD-2-PA as the membrane. The flux from the **patch** remained roughly constant at about 45-50 mu g/cm.sup.2 .multidot.h.

DETD For Example 24, the monolith contained 37 mg of nicotine, with a **patch** area of 5 cm.sup.2. For Example 25, the monolith contained 74 mg of nicotine, with a **patch** area of 10 cm.sup.2. For Example 26, the monolith contained 60 mg of nicotine, with a **patch** area of 20 cm.sup.2. For Example 27, the monolith contained 54 mg of nicotine, with a **patch** area of 30 cm.sup.2.

DETD . . . systems used were manufactured as described in Examples 24-27, and each contained a total of 37 mg nicotine in a **patch** with an area of 5 cm.sup.2, as in Example 24. For Example 28, a single 5 cm.sup.2 transdermal nicotine **patch** was applied to the right forearm of each subject, and the **patch** remained affixed to the forearm for 16 hours. The lowest curve presents the average nicotine plasma level obtained. For Example. . .

DETD . . . state pharmacokinetics of the 22 and 27 mg patches of the present invention with the PROSTEP 22 mg transdermal nicotine **patch**, available from elan pharma, Ltd., Athlone, County Westmeath, Ireland, and manufactured by Lederle Laboratories Division, American Cyanamid Company, Pearl River,. . .

DETD . . . five consecutive days of the treatment period. The resulting blood plasma levels, along with those of the PROSTEP 22 mg **patch** are shown in FIG. 14. The patches of the present invention were well tolerated.

DETD TABLE VI

Transdermal **Patch**.sup.5	Cmax.sup.6 (ng/mL)	Cavg.sup.7 (ng/mL)	Cmin.sup.8 (ng/mL)	Tmax.sup.9 (hrs)
Habitrol .TM. (21 mg/day).sup.10	17 .+-. 2	13 .+-. 2	9 .+-. 2	6 .+-. 3
PROSTEP .TM. (21 mg/day)	16. . .	11 .+-. 3		4 .+-. 3
NICOTROL .SM.	13.0 .+-. 3.1	8.7 .+-. 2.1	2.5 .+-. 0.8	8 .+-. 3

(15 mg/day)
PATCH OF 16.1 .+-. 7.1
11.2 .+-. 4.1
4.8 .+-. 1.8
8.4 .+-. 1.8

EXAMPLE 1
(22 mg/day)
PATCH OF 23.4 .+-. 8.1
14.5 .+-. 3.3
5.7 .+-. 1.9
8.4 .+-. 3.3

EXAMPLE 2
(27 mg/day)

.sup.5 Competitor product data taken. . .
CLM What is claimed is:
. . . skin-distal side, the depot layer containing a sufficient quantity of
nicotine to maintain a useful flux of nicotine from the **patch** for a total time period of 12 hours or more; ii) an occlusive backing layer in contact with and covering. . .

L8 ANSWER 4 OF 9 USPATFULL
AN 97:120298 USPATFULL
TI Water-soluble pressure-sensitive mucoadhesive and devices provided therewith for emplacement in a mucosa-lined body cavity
IN Biegajski, James E., Foster City, CA, United States
Venkatraman, Subbu S., Palo Alto, CA, United States
Scott, Ann M., Mountain View, CA, United States
PA Cygnus, Inc., Redwood City, CA, United States (U.S. corporation)
PI US 5700478 19971223
WO 9505416 19950223
AI US 1995-505185 19950803 (8)
WO 1994-US9305 19940819
19950803 PCT 371 date
19950803 PCT 102(e) date
DT Utility
FS Granted
EXNAM Primary Examiner: Azpuru, Carlos A.
LREP Morrison & Foerster LLP
CLMN Number of Claims: 45
ECL Exemplary Claim: 1
DRWN 17 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 2104
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Water-soluble pressure-sensitive adhesives include a water-soluble polymer that is made tacky at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer. Suitable polymers are solid at room temperature; and have a hydrophilicity as measured by water uptake greater than about 25%; they are liquid at room temperature and have a boiling point higher than about 80.degree. C. The adhesives according to the invention may conveniently be provided in dry film form. Preferred water-soluble pressure-sensitive adhesives of the invention adhere both to mucosal surfaces and to a variety of materials that may constitute a part of a device or prosthesis to be held in a body cavity that has a mucosal lining. Also, a laminated device for the controlled release of a substance within a mucosa-lined body cavity

includes the substance dissolved or dispersed in either or both of a water-soluble pressure-sensitive adhesive layer and optionally one or more water-soluble polymer layers. Also, devices for administering a substance over an extended time for relief of sore throat or cough, or for administering a breath freshening agent, particularly a mint odorant, include a water soluble polymer film layer containing the active ingredient, and a water soluble pressure sensitive mucoadhesive layer.

SUMM . . . No. 4,948,580 describes a bioadhesive composition for delivery of anti-bacterials, including a copolymer of ("PVME/MA"), and gelatin, dispersed in an **ointment** base.

SUMM . . . or tablet form, may be used. For relief of cough, for example, substances such as dextromethorphan HBr, noscpine, codeine phosphate, **menthol**, and the like, may be used. Further, both a sore throat medication and a cough suppressant can be combined within. . .

SUMM . . . can be used as part of a system for delivery of substances through the oral mucosa (as a buccal transmucosal **patch**), or for delivery of substances into the oral cavity itself.

SUMM . . . disperses within the oral cavity. Such additional ingredients include, for example, sweeteners such as aspartame, and breath fresheners such as **menthol**.

SUMM In some embodiments the odorant is an **essential oil** of a plant material, or a refined fraction of an **essential oil**, or a combination of the chief aromatic constituents of an **essential oil**. Preferably the odorant is a mint odorant. We have discovered that, surprisingly, the essential oils that are commonly used as. . .

DRWD FIG. 17 is a graph comparing **menthol** release over time from a breath freshening device according to the invention and from a conventional commercially marketed "breath mint"(Certs.RTM.).

DETD . . . other flavors, deodorants such as for example the odor-preventive antimicrobial CPC, anti-bacterials such as chlorhexidine, sore-throat medicants such as Hexylresorcinol/Phenol derivatives/**Menthol**, cough suppressants such as Dextrathomorphan Hydochloride, agents to prevent mouth dryness, benzocaine for treatment of rhinitis, etc.

DETD . . . alternatively) act to inhibit crystallization of some active substances that might otherwise occur at the loading concentrations employed (for example, **menthol**).

DETD

Glycerin	1.0 grams
Cineole	1.0 grams
Aspartame	0.3 grams
Menthol	1.7 grams
HPC Klucel LF	16 grams

DETD . . . have an active substance-containing layer weighing approximately 100 milligrams. Such a layer (and the disc) therefore contains 8.5 milligrams of **menthol** and 5 milligrams of cineole.

DETD

Glycerin	2.0 grams
Dyclonine HCl	0.6 grams
Menthol	1.0 grams
Aspartame	0.3 grams
HPC Klucel LF	16.1 grams

DETD . . . have an active substance-containing layer weighing approximately 100 milligrams. Such a layer (and the disc) therefore contains 5 mg of **menthol** and 3 mg of Dyclonine HCl.

DETD . . . particular flavor, even where the flavor that is recalled is in
fact complex. Such character impact compounds include, for example, **Menthol** (having the character impact of peppermint); L-Carvone (spearmint); Methyl salicylate (wintergreen); and Citral (lemon).

DETD . . . layer of a breath freshening device according to the invention is to add to the polymer of the layer an **essential oil** (i.e., a volatile oil) of a plant material. The Source Book of Flavors describes essential oils that are in common. . .

DETD . . . the Source Book of Flavors. They include, particularly for example, oil of peppermint, the chief aromatic constituents of which are
menthol, merithone, and menthyl acetate; oil of spearmint, the chief aromatic constituent of which is L-Carvone; and oil of wintergreen, the. . .

DETD

menthofuran (GLC)	02.6%
menthol	57.0
menthone	24.8
menthyl acetate	07.4

DETD "310-30B#2": 40% RPC HF; 35.5% PVP 90 F; 20% RPC LF; 2% Mentha Oil; 2% **Menthol**; 0.5% Fennel Oil (described in Hisahige JP 63-209797).

DETD "310-44" 44.5% PVP 90 F; 30% HPC LF; 10% RPC RF; 10% PEG 400; 2.5% **Menthol**; 2.0% Mentha Oil; 1.0% Fennel Oil (described in Hisahige JP 63-209797).

DETD . . . described in Example XVII. Portions of the film 1/2 inch in diameter and 25 mils thick, each containing 8.6 mg **menthol** were immersed in distilled water, and breath mint tablets each containing 4.3 mg **menthol** were immersed in distilled water in separate flasks, and the flasks were continuously shaken. Samples were withdrawn from the flasks after elapsed times of 15 min., 30 min., 45 min., 60 min., and 120 min., and the quantity of **menthol** was analyzed by gas chromatography.

DETD . . . average, the breath freshening device of the invention had by the first (fifteen minute) sample interval released about 0.7 mg **menthol**, and thereafter the device delivered **menthol** at a continuous steady rate throughout the sampling period; at the two hour sampling interval, approximately 2.0 mg of the original 8.6 mg of **menthol** had been released from the device, and rate of delivery was continuing at slightly less than 0.25 mg per hour.. . . By contrast, each breath mint had on average by the first sampling interval
released nearly half its total quantity of **menthol**, and had nearly exhausted their delivery capacity at the second (thirty minute) sampling interval.

DETD . . . and a flavor imparting a different taste or odor can be added instead. Also, the loading of actives dydonine HCl, **menthol**, and cineole can be controlled by either varying the concentration or changing the thickness of the disc. Other active substances. . .

CLM What is claimed is:
. . . composite of claim 26 wherein the active ingredient is selected from the group consisting of dextromethorphan HBR, nospine, codeine phosphate, **menthol**.

L8 ANSWER 5 OF 9 USPATFULL
AN 97:3536 USPATFULL
TI Method and therapeutic system for smoking cessation

IN Baker, Richard W., Palo Alto, CA, United States
Santus, Giancarlo, Milan, Italy
Vintilla-Friedman, Susan, Cupertino, CA, United States
PA Pharmacia AB, Sweden (non-U.S. corporation)
PI US 5593684 19970114
AI US 1994-221914 19940331 (8)
RLI Continuation of Ser. No. US 1993-103262, filed on 4 Aug 1993, now patented, Pat. No. US 5362496
DT Utility
FS Granted
EXNAM Primary Examiner: Criares, Theodore J.
LREP Pravel, Hewitt, Kimball & Krieger
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN 14 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 2219
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for treating conditions responsive to nicotine therapy, and particularly for smoking cessation therapy and for reducing nicotine craving, is described that utilizes transdermal nicotine delivery for obtaining base-line nicotine plasma levels coupled with transmucosal administration of nicotine to satisfy transient craving.
SUMM . . . Studies using human cadaver skin in vitro are likewise consistent with this finding. Typical permeabilities during the first day of **patch** use are on the order of 0.1 mg/cm.sup.2 .multidot.h, increasing to 0.4 mg/cm.sup.2 .multidot.h and more at later times. Systemic. . .
SUMM . . . 1:7-10 reported on the results of a double-blind study in which they determined that long-term use of a transdermal nicotine **patch** significantly increased the quit rate in cigarette smokers. The results of this study showed that the number of abstainers in. . . group. In another study reported by Mulligan et al. (1990) Clin. Pharmacol. Ther. 47:331-337, the use of a transdermal nicotine **patch** in a 6-week placebo-controlled double-blind study resulted in a significant degree of smoking cessation. Finally, a report by Rose et. . .
SUMM . . . skin-distal side, the depot layer containing a sufficient quantity of nicotine to maintain a useful flux of nicotine from the **patch** for a total time period of 12 hours or more;
SUMM According to other embodiments, the **patch** may take the form of a reservoir system, in which the depot of nicotine is separated from the skin by a nonporous polymeric membrane, through which the nicotine diffuses at a controlled rate. The **patch** may also be in the form of a monolithic matrix, consisting of a single phase solution or mixture of nicotine. . .
DRWD FIG. 6 is a graph of nicotine delivery (mg/cm.sup.2) through 100-micron thick Elvax 880 membranes, from a **patch** containing 200 mu L pure nicotine, with a membrane area of 4.5 cm.sup.2, as a function of time (hr).
DRWD FIG. 7 is a graph of nicotine delivery (mg/cm.sup.2) through 100-micron thick Elvax 88 membranes, from a **patch** containing 200 mu L of a 5% suspension of nicotine in a 20 wt sodium sulfate solution, with a membrane. . .
DRWD . . . patches with nylon or polyethylene membranes, as a function of time (hr). The nicotine content is 20-25 mg, and the **patch** area is 3.9 cm.sup.2.
DRWD . . . the present invention delivering either 22 mg (.quadrature.) or

27 mg (o) of nicotine or the PROSTEP 22 mg (.box-solid.) **patch** as a function of time (hr) .

DETD "**Essential oil**" refers to a natural oil with a distinctive scent secreted by the glands of certain aromatic plants having terpenes as. . .

DETD . . . nicotine system described in the present invention is shown in FIG. 2. Referring now to this figure, the nicotine dispensing **patch**, 1, comprises an impermeable backing layer, 2, and a monolithic matrix layer, 3, which both serves as a depot for. . .

DETD The impermeable backing layer, 2, defines the nonskin facing, or skin distal, side of the **patch** in use. The functions of the backing layer are to provide an occlusive layer that prevents loss of nicotine to the environment, and to protect the **patch**. The material chosen should therefore be nicotine resistant, and should exhibit minimal nicotine permeability. The backing layer should be opaque,. . .

DETD . . . in theory patches of this type with a bigger load can be made. Also, the amount of nicotine in the **patch** as made may exceed the delivered load because, as the **patch** becomes exhausted, there will be an insufficient concentration gradient to remove all the nicotine. Consequently, the activity of the **patch** may fall below useful levels.

DETD . . . elimination of skin irritation. The release mechanism for the nicotine is diffusion under a concentration gradient. Therefore, even if the **patch** were to be ingested, the nicotine release would be still a gradual process, and the victim would not be exposed. . .

DETD To ensure that a user cannot be exposed to a toxic dose when the **patch** is used correctly, the in vitro nicotine flux from the **patch** must stay within certain limits. This is a much more critical issue with nicotine than with most drugs, because nicotine. . . 20-fold or more between individuals and between different skin sites on the same individual. It is thus clear that a **patch** with a large nicotine load must be able to control release of that load, such that the in vitro flux from the **patch** does not exceed about 10 times, preferably about 5 times, and more preferably about equals, the average skin permeation rate. Of course, embodiments where the in vitro flux from the **patch** is less than the skin permeation rate, such that the systemic absorption is controlled primarily by the **patch** rather than the skin, are acceptable, so long as the systemic nicotine level can be sustained above the necessary minimum.

DETD . . . by means of a porous or nonporous overlay coated wholly or partly with adhesive, by an adhesive layer between the **patch** and skin, or by an annulus of adhesive around the periphery of the **patch**. Of course, the mixed reservoir/monolith embodiments with adhesive medical tapes do not require additional adhesive.

DETD If an adhesive layer is to be included as an integral part of the **patch**, the adhesive should be nicotine compatible and permit a useful nicotine flux. In addition, the adhesive should satisfy the general. . .

DETD Loss of nicotine from the **patch** after manufacture should be kept to a minimum. Normally, the skin-facing side of the **patch** will be covered with a peel strip until the **patch** is used. As stressed throughout, nicotine is volatile, and retention of the nicotine load within the **patch** during storage requires that the outer **patch** layers be extremely nicotine-resistant and nicotine-impermeable. The peel strip therefore should possess the same

properties as the backing layer, and. . .

DETD According to a particularly preferred embodiment, the transdermal nicotine **patch** will comprise a rounded-rectangular, "skin tone" colored **patch** on a clear, rectangular release liner. More specifically, the **patch** will comprise a flexible, occlusive film backing, a multilaminate matrix containing nicotine, a skin adhesive layer, and a protective release. . .

DETD Another embodiment of the invention is shown in FIG. 3. Referring now to this figure, the nicotine dispensing **patch**, 4, comprises an impermeable backing layer, 2, a nicotine reservoir, 5, and a polymer membrane, 6. The backing layer may. . .

DETD . . . layer. The reservoir layer does not contribute to any measurable extent to the rate-controlling mechanism. To discourage tampering with the **patch**, or misuse of the contents, it may be desirable to mix the nicotine with other materials as described in U.S..

. .

DETD If the **patch** is to be loaded with a comparatively small quantity of nicotine, then the nicotine can be conveniently kept in contact. . . can be used. The disk also decreases the user's risk of exposure to a high dose of nicotine should the **patch** become accidentally ruptured.

DETD The polymer membrane layer, 6, is the rate-controlling means that regulates the flux of nicotine from the **patch** to the skin. The criteria for selection of a suitable material are those discussed in the background section above, namely. . . should also be compatible with the other components, and workable by standard techniques that are used in fabrication of the **patch**, such as casting or heat sealing.

DETD Dense nonporous membranes have a substantial advantage over microporous materials. Microporous membranes release the contents of the **patch** by pore flow. Thus, in areas of the pores, the skin is exposed to raw nicotine. Also, in the case. . . so that the system is quickly exhausted, and the skin is flooded with excess nicotine for the life of the **patch**. In contrast, diffusion of nicotine through a nonporous film takes place by dissolution of the nicotine in the film, followed. . .

DETD Alternatively, it may be possible to purchase the membrane already in film form. This type of transdermal **patch** may be prepared by heat-sealing the backing to the membrane layer around the perimeter of the **patch**. The nicotine formulation may be added either before or after heat sealing. If the formulation is added before heat sealing,.

. .

DETD . . . the reservoir side of the membrane, the nicotine flux through the membrane remains relatively constant over the life of the **patch**.

DETD . . . discussed above, these kinds of considerations matter more when dispensing nicotine than with many other substances. Suppose that a transdermal **patch**, tested in vitro, delivers a substantial fraction of its total drug load during the first few hours, at a flux. . . The in vitro flux then falls off to levels that are well below the average skin permeation rate until the **patch** is exhausted. When this **patch** is applied to the user, the skin will be saturated with drug and the drug will pass through the skin. . .

DETD . . . depot" phenomenon may be perfectly acceptable, or even preferable, since it tends to balance out the falling flux from the **patch**.

DETD . . . patches currently available exhibit this effect and function satisfactorily in this way. However, for nicotine, the situation is different. A **patch** that can avoid this high initial drug burst, with consequent skin irritation or risk of overdose, is desirable. Any initial flux from the **patch** should not exceed a maximum of 2 mg/cm.sup.2 .multidot.h, and more preferably should not exceed 1 mg/cm.sup.2 .multidot.h. Any flux. . . of the patient, and the drug flux required, it may be easier to stay within this limit with a reservoir-type **patch**. The risk of accidental overdose if the **patch** is damaged or ingested, however, is minimized with monolithic embodiments. There will therefore be circumstances where one or the other type of **patch** is preferably indicated.

DETD . . . in FIG. 4 exploits the advantages of both reservoir and monolith systems. Referring now to this figure, the nicotine dispensing **patch**, 7, comprises an impermeable backing layer, 2, a monolithic matrix layer, 3, and a polymer membrane layer, 8. The backing. . .

DETD . . . than the monolith material, so that the adhesive layer serves as a thin membrane limiting flux of nicotine from the **patch**.

DETD . . . from 3M Company. The additional resistance to permeation created by the tape assists in holding the nicotine load in the **patch** and moderates the initial high drug flux.

DETD . . . an overdose of nicotine is reduced, because the monolith cannot release its nicotine load in a single burst if the **patch** is damaged or even swallowed.

DETD . . . and 4,920,989, each of which is expressly incorporated herein by reference. More specifically, according to one embodiment, a transdermal nicotine **patch** similar to the PROSTEP.SM. will be employed. This **patch** comprises, proceeding from the visible outer surface toward the inner surface attached to the skin, (1) a foam tape and. . .

DETD Alternatively, a nicotine **patch** similar to the Habitrol.SM. **patch** can be used. This **patch** comprises, proceeding from the visible outer surface toward the inner surface attached to the skin, (1) an aluminized-backing film; (2). . .

DETD Other embodiments will employ a nicotine **patch** similar to the Nicoderm.RTM. nicotine transdermal system, available from ALZA Corporation, Palo Alto, Calif. This **patch** is a multilayered rectangular film containing nicotine as the active agent. Proceeding from the visible surface toward the surface attached. . .

DETD E. **Patch** Specifications

DETD The transdermal nicotine **patch** provides a base line or steady state nicotine level to the patient. The total amount of nicotine released by the **patch** during the period of use will vary depending on the user's body size, history of exposure to nicotine, and response. . .

DETD General guidelines for **patch** design must ensure that the patient is protected at all times from toxic doses of nicotine, and must also ensure. . . receives a dose of nicotine that will be effective for smoking cessation therapy. The in vitro flux from any individual **patch** used for the intended therapy should remain below about 800 mu g/cm.sup.2 .multidot.h, preferably below 600 mu g/cm.sup.2 .multidot.h, and more preferably below 400 mu g/cm.sup.2 .multidot.h during the life of the **patch**. Staying within these limits ensures that a patient with unusually permeable skin can never receive a

toxic dose.

DETD The size of the **patch** will vary according to the amount of nicotine to be delivered. To deliver 25 mg in a 24-hour period, the **patch** would have a skin-contacting area of about 15-30 cm.sup.2. To maximize patient acceptance and compliance, and to minimize any skin irritation, the **patch** size should not exceed about 45 cm.sup.2 maximum skin covering area. With the systems and release characteristics taught by applicant, it should be possible to keep the **patch** size in the range 1-50 cm.sup.2, preferably 20-35 cm.sup.2.

DETD . . . reduces immediate metabolism by the liver and intestinal wall flora. Oral drug dosage forms (e.g., lozenge, capsule, gum, tablet, suppository, **ointment**, gel, pessary, membrane, and powder) are typically held in contact with the mucosal membrane and disintegrate and/or dissolve rapidly to. . .

DETD . . . vanilla, and the like; essential oils such as peppermint, spearmint and the like; or other flavor, such as aniseed, eucalyptus, 1-**menthol**, carvone, anethole and the like, to mask the taste of nicotine. See Hall et al. Food Technol. 14:488 (1960); 15:20. . .

DETD . . . the production of inclusion complexes of both the nicotine and the flavorant. This embodiment is employed, for example, when an **essential oil**, or other volatile flavorant, such as carvone or **menthol**, is used in the lozenge formulation. As in the case of the nicotine inclusion complexes described herein, incorporation of the. . .

DETD Whereas the **patch** serves to provide a base line or steady state nicotine level, the transmucosal administration of nicotine provides periodic transient blood. . .

DETD . . . base line level of nicotine plasma level. The present invention fulfills this objective through the use of a transdermal nicotine **patch** in combination with the transmucosal administration of nicotine, and preferably the administration of nicotine through the oral mucosa, and most preferably, with nicotine lozenges. The transdermal **patch** and the transmucosal administration of nicotine operate in a complimentary manner with the transdermal **patch** providing the steady-state systemic levels of nicotine in the bloodstream to which the smoker has become accustomed, whereas the transmucosal. . .

DETD . . . for an individualized approach to smoking cessation therapy. Specifically, the total amount of nicotine delivered, the delivery mode, i.e., via **patch** or transmucosal delivery method and regimen, i.e., the order of administration and duration of use of either the **patch** and/or the transmucosal delivery formulation, can be varied to take into account the patient's needs, e.g., the therapeutic indication, the. . .

DETD For example, according to one embodiment, the transdermal **patch** and transmucosal administration of nicotine are first used concurrently and simultaneously for a period of from about 3 to 12. . . preferably from about 4 to 8 weeks, and most preferably from about 4 to 6 weeks, in which only the **patch** or only the transmucosal nicotine formulation is used.

DETD Other embodiments will employ different dosage levels of either the **patch** and/or the transmucosal nicotine formulation to suit the needs of those patients with either a relatively high or low nicotine.

. . more on the Fagerstrom test, will typically consist of three phases. During the initial phase, a high dosage nicotine transdermal **patch**, typically, with a high loading of nicotine in the range of about 30-60 mg, and preferably, about 40-45 mg, is. . . from about 4 to 8 weeks. Typically, transmucosal administration of nicotine will be used in conjunction with this high dosage **patch**. Subsequently, a transdermal **patch** with a lower loading of nicotine, typically in the range of about 10-30 mg, and preferably, about 20-25 mg, and. . . of from about 4 to 8 weeks. Finally, for a period of from about 4 to 6 weeks, either the **patch** or the transmucosal administration of nicotine may be used alone.

DETD . . . moderate smoker, i.e., those scoring 6 or less on the Fagerstrom test. For example, during the initial phase, a transdermal **patch** with a moderate loading of nicotine, typically in the range of about 10-40 mg, and preferably, about 25-30 mg, is. . . administration of nicotine. The second phase of this smoking cessation program will consist of administration of a lower dosage transdermal **patch**, typically containing nicotine in the range of about 10-30 mg, and preferably, about 20-25 mg, optionally, with the transmucosal administration. . . used for a period of from about 4 to 8 weeks. During the final phase or weaning period, either the **patch** or transmucosal administration will be used alone.

DETD . . . cessation program for the light smoker can be developed using the compositions and methods described herein. For example, a transdermal **patch** containing a relatively low loading of nicotine, typically containing nicotine in the range of about 10-30 mg, and preferably, about. . . used for a period of from about 4 to 8 weeks. During the final phase or weaning period, either the **patch** or the transmucosal formulation will be used alone.

DETD . . . cigarette smoking. Thus, and with many patients, it is possible to reduce the incidence of smoking with either the transdermal **patch** or the transmucosal formulation alone.

DETD TABLE III

Property	Low Dosage **Patch**	High Dosage **Patch**
Dosage Strength	22 mg/20 cm.sup.2	27 mg/20 cm.sup.2
Size (cm.sup.2)	20	20
Nicotine content (mg)	31.4	37.7
24 Hour Delivery (mg).sup.2	22	27
Fluz (mg/cm.sup.2 /24 hour).sup.3	1.1	1.35
Total Nicotine Delivered (%)	73	75
Patch Weight (mg)	837	843

Thickness (micron)	333	344

.sup.2 Based on residual content from in vivo performance.
.sup.3 Estimated from in vivo performance.

DETD TABLE IV

Composition	Nicotine **Patch** A	Nicotine **Patch** B
Dosage	22 mg/20 cm2	27 mg/20 cm2
Nicotine content (mg)	31.4	37.7
Acrylic adhesive matrix (mg)	70.2	70.2
Butylated hydroxytoluene (mg)	0.6	0.6
Polyester film	76.0. . .	

DETD The **patch**-making procedure and release tests described in Example 9 were repeated using the same membrane, but with a load of 200.
. .

DETD The **patch**-making procedure and release tests described in Example 11 were repeated with a 22- mu m thick film of Sclairfilm HD-2-PA as the membrane. The flux from the **patch** remained roughly constant at about 80 mu g/cm.sup.2 .multidot.h for the first 60 hours, falling to about 30 mu g/cm.sup.2. . .

DETD The **patch**-making procedure and release tests described in Example 11 were repeated with a 50- mu m thick film of Sclairfilm LWS-2-PA as the membrane. The flux from the **patch** remained roughly constant at about 45-50 mu g/cm.sup.2 .multidot.h.

DETD For Example 24, the monolith contained 37 mg of nicotine, with a **patch** area of 5 cm.sup.2. For Example 25, the monolith contained 74 mg of nicotine, with a **patch** area of 10 cm.sup.2. For Example 26, the monolith contained 60 mg of nicotine, with a **patch** area of 20 cm.sup.2. For Example 27, the monolith contained 54 mg of nicotine, with a **patch** area of 30 cm.sup.2
.

DETD . . . systems used were manufactured as described in Examples 24-27, and each contained a total of 37 mg nicotine in a **patch** with an area of 5 cm.sup.2, as in Example 24. For Example 28, a single 5 cm.sup.2 transdermal nicotine **patch** was applied to the right forearm of each subject, and the **patch** remained affixed to the forearm for 16 hours. The lowest curve presents the average nicotine plasma level obtained. For Example. . .

DETD . . . state pharmacokinetics of the 22 and 27 mg patches of the present invention with the PROSTEP 22 mg transdermal nicotine **patch**, available from elan pharma, Ltd., Athlone, County Westmeath, Ireland, and manufactured by Lederle Laboratories Division, American Cyanamid Company, Pearl River,. . .

DETD . . . five consecutive days of the treatment period. The resulting blood plasma levels, along with those of the PROSTEP 22 mg **patch** are shown in FIG. 14. The patches of the present invention were well tolerated.

DETD TABLE VI

Transdermal	Cmax.sup.6

	Cavg.sup.7	Cmin.sup.8	Tmax.sup.9
Patch.sup.5	(ng/mL)	(ng/mL)	(hrs)
Habitrol .TM.	17 .+-. 2	13 .+-. 2	9 .+-. 2
			6 .+-. 3
(21 mg/day).sup.10			
PROSTEP .TM.	16 .+-..	. .	4 11.+-. 3
			4 .+-. 3
(21 mg/day)			
NICOTROL .SM.	13.0 .+-. 3.1		
	8.7 .+-. 2.1		
		2.5 .+-. 0.8	
			8 .+-. 3
(15 mg/day)			
PATCH OF	16.1 .+-. 7.1		
	11.2 .+-. 4.1		
		4.8 .+-. 1.8	
			8.4 .+-. 1.8
EXAMPLE 1			
(22 mg/day)			
PATCH OF	23.4 .+-. 8.1		
	14.5 .+-. 3.3		
		5.7 .+-. 1.9	
			8.4 .+-. 3.3
EXAMPLE 2			
(27 mg/day)			

.sup.5 Competitor product data taken. . .

CLM What is claimed is:

. . . skin-distal side, the depot layer containing a sufficient quantity of

nicotine to maintain a useful flux of nicotine from the **patch** for a total time period of 12 hours or more; (b) an occlusive backing layer in contact with and covering. . .

L8 ANSWER 6 OF 9 USPATFULL

AN 94:97336 USPATFULL

TI Method and therapeutic system for smoking cessation

IN Baker, Richard W., Palo Alto, CA, United States
Santus, Giancarlo, Milan, Italy
Vintilla-Friedman, Susan, Cupertino, CA, United States

PA Pharmetrix Corporation, Menlo Park, CA, United States (U.S. corporation)

PI	US 5362496	19941108
AI	US 1993-103262	19930804 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Cintins, Marianne M.; Assistant Examiner: Criares, T. J.

LREP Townsend and Townsend Khourie and Crew

CLMN Number of Claims: 12

ECL Exemplary Claim: 1

DRWN 14 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 2150
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for treating conditions responsive to nicotine therapy, and particularly for smoking cessation therapy and for reducing nicotine craving, is described that utilizes transdermal nicotine delivery for obtaining base-line nicotine plasma levels coupled with transmucosal administration of nicotine to satisfy transient craving.

SUMM . . . Studies using human cadaver skin in vitro are likewise consistent with this finding. Typical permeabilities during the first day of **patch** use are on the order of 0.1 mg/cm.sup.2 .multidot.h, increasing to 0.4 mg/cm.sup.2 .multidot.h and more at later times. Systemic. . .

SUMM . . . 1:7-10 reported on the results of a double-blind study in which they determined that long-term use of a transdermal nicotine **patch** significantly increased the quit rate in cigarette smokers. The results of this study showed that the number of abstainers in. . . group. In another study reported by Mulligan et al. (1990) Clin. Pharmacol. Ther. 47:331-337, the use of a transdermal nicotine **patch** in a 6-week placebo-controlled double-blind study resulted in a significant degree of smoking cessation. Finally, a report by Rose et. . .

SUMM . . . skin-distal side, the depot layer containing a sufficient quantity of nicotine to maintain a useful flux of nicotine from the **patch** for a total time period of 12 hours or more;

SUMM According to other embodiments, the **patch** may take the form of a reservoir system, in which the depot of nicotine is separated from the skin by a nonporous polymeric membrane, through which the nicotine diffuses at a controlled rate. The **patch** may also be in the form of a monolithic matrix, consisting of a single phase solution or mixture of nicotine. . .

DRWD FIG. 6 is a graph of nicotine delivery (mg/cm.sup.2) through 100-micron thick Elvax 880 membranes, from a **patch** containing 200 mu L pure nicotine, with a membrane area of 4.5 cm.sup.2, as a function of time (hr).

DRWD FIG. 7 is a graph of nicotine delivery (mg/cm.sup.2) through 100-micron thick Elvax 88 membranes, from a **patch** containing 200 mu L of a 5% suspension of nicotine in a 20 wt % sodium sulfate solution, with a. . .

DRWD . . . patches with nylon or polyethylene membranes, as a function of time (hr). The nicotine content is 20-25 mg, and the **patch** area is 3.9 cm.sup.2.

DRWD . . . present invention delivering either 22 mg (.quadrature.) or 27 mg (O) of nicotine or the PROSTEP 22 mg ( ) **patch** as a function of time (hr).

DRWD "**Essential oil**" refers to a natural oil with a distinctive scent secreted by the glands of certain aromatic plants having terpenes as. . .

DRWD . . . nicotine system described in the present invention is shown in FIG. 2. Referring now to this figure, the nicotine dispensing **patch**, 1, comprises an impermeable backing layer, 2, and a monolithic matrix layer, 3, which both serves as a depot for. . .

DRWD The impermeable backing layer, 2, defines the non-skin facing, or skin distal, side of the **patch** in use. The functions of the backing layer are to provide an occlusive layer that prevents loss of nicotine to the environment, and to protect the **patch**. The material chosen should therefore be nicotine resistant, and should exhibit

minimal nicotine permeability. The backing layer should be opaque,. .
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DRWD . . . in theory patches of this type with a bigger load can be made. Also, the amount of nicotine in the **patch** as made may exceed the delivered load because, as the **patch** becomes exhausted, there will be an insufficient concentration gradient to remove all the nicotine. Consequently, the activity of the **patch** may fall below useful levels.
DRWD . . . elimination of skin irritation. The release mechanism for the nicotine is diffusion under a concentration gradient. Therefore, even if the **patch** were to be ingested, the nicotine release would be still a gradual process, and the victim would not be exposed. . .
DRWD To ensure that a user cannot be exposed to a toxic dose when the **patch** is used correctly, the in vitro nicotine flux from the **patch** must stay within certain limits. This is a much more critical issue with nicotine than with most drugs, because nicotine. . . 20-fold or more between individuals and between different skin sites on the same individual. It is thus clear that a **patch** with a large nicotine load must be able to control release of that load, such that the in vitro flux from the **patch** does not exceed about 10 times, preferably about 5 times, and more preferably about equals, the average skin permeation rate. Of course, embodiments where the in vitro flux from the **patch** is less than the skin permeation rate, such that the systemic absorption is controlled primarily by the **patch** rather than the skin, are acceptable, so long as the systemic nicotine level can be sustained above the necessary minimum.

.
.
DRWD . . . by means of a porous or nonporous overlay coated wholly or partly with adhesive, by an adhesive layer between the **patch** and skin, or by an annulus of adhesive around the periphery of the **patch**. Of course, the mixed reservoir/monolith embodiments with adhesive medical tapes do not require additional adhesive.
DRWD If an adhesive layer is to be included as an integral part of the **patch**, the adhesive should be nicotine compatible and permit a useful nicotine flux. In addition, the adhesive should satisfy the general. . .
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DRWD According to a particularly preferred embodiment, the transdermal nicotine **patch** will comprise a rounded-rectangular, "skin tone" colored **patch** on a clear, rectangular release liner. More specifically, the **patch** will comprise a flexible, occlusive film backing, a multilaminate matrix containing nicotine, a skin adhesive layer, and a protective release. . .
DRWD Another embodiment of the invention is shown in FIG. 3. Referring now to this figure, the nicotine dispensing **patch**, 4, comprises an impermeable backing layer, 2, a nicotine reservoir, 5, and a polymer membrane, 6. The backing layer may. . .
DRWD . . . layer. The reservoir layer does not contribute to any measurable extent to the rate-controlling mechanism. To discourage

tampering with the **patch**, or misuse of the contents, it may be desirable to mix the nicotine with other materials as described in U.S..

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DRWD If the **patch** is to be loaded with a comparatively small quantity of nicotine, then the nicotine can be conveniently kept in contact. . . can be used. The disk also decreases the user's risk of exposure to a high dose of nicotine should the **patch** become accidentally ruptured.

DRWD The polymer membrane layer, 6, is the rate-controlling means that regulates the flux of nicotine from the **patch** to the skin. The criteria for selection of a suitable material are those discussed in the background section above, namely. . . should also be compatible with the other components, and workable by standard techniques that are used in fabrication of the **patch**, such as casting or heat sealing.

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DRWD Alternatively, it may be possible to purchase the membrane already in film form. This type of transdermal **patch** may be prepared by heat-sealing the backing to the membrane layer around the perimeter of the **patch**. The nicotine formulation may be added either before or after heat sealing. If the formulation is added before heat sealing,.

. .

DRWD . . . the reservoir side of the membrane, the nicotine flux through the membrane remains relatively constant over the life of the **patch**.

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or the other type of **patch** is preferably indicated.

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DRWD E. **Patch** Specifications

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DRWD General guidelines for **patch** design must ensure that the patient is protected at all times from toxic doses of nicotine, and must also ensure. . . receives a dose of nicotine that will be effective for smoking cessation therapy. The in vitro flux from any individual **patch** used for the intended therapy should remain below about 800 mu g/cm.sup.2 .multidot.h, preferably below 600 mu g/cm.sup.2 .multidot.h, and more preferably below 400 mu g/cm.sup.2 .multidot.h during the life of the **patch**. Staying within these limits ensures that a patient with unusually permeable skin can never receive a toxic dose.

DRWD The size of the **patch** will vary according to the amount of nicotine to be delivered. To deliver 25 mg in a 24-hour period, the **patch** would have a skin-contacting area of about 15-30 cm.sup.2. To maximize patient acceptance and compliance, and to minimize any skin irritation, the **patch** size should not exceed about 45 cm.sup.2 maximum skin covering area. With the systems and release characteristics taught by applicant, it should be possible to keep the **patch** size in the range 1-50 cm.sup.2 preferably 20-35 cm.sup.2.

DRWD . . . reduces immediate metabolism by the liver and intestinal wall flora. Oral drug dosage forms (e.g., lozenge, capsule, gum, tablet, suppository, **ointment**, gel, pessary, membrane, and powder) are

typically held in contact with the mucosal membrane and disintegrate and/or dissolve rapidly to. . .

DRWD . . . vanilla, and the like; essential oils such as peppermint, spearmint and the like; or other flavor, such as aniseed, eucalyptus, 1-**menthol**, carvone, anethole and the like, to mask the taste of nicotine. See Hall et al. Food Technol. 14:488 (1960); 15:20. . .

DRWD . . . the production of inclusion complexes of both the nicotine and the flavorant. This embodiment is employed, for example, when an **essential oil**, or other volatile flavorant, such as carvone or **menthol**, is used in the lozenge formulation. As in the case of the nicotine inclusion complexes described herein, incorporation of the. . .

DRWD Whereas the **patch** serves to provide a base line or steady state nicotine level, the transmucosal administration of nicotine provides periodic transient blood. . .

DRWD . . . base line level of nicotine plasma level. The present invention fulfills this objective through the use of a transdermal nicotine **patch** in combination with the transmucosal administration of nicotine, and preferably the administration of nicotine through the oral mucosa, and most preferably, with nicotine lozenges. The transdermal **patch** and the transmucosal administration of nicotine operate in a complimentary manner with the transdermal **patch** providing the steady-state systemic levels of nicotine in the bloodstream to which the smoker has become accustomed, whereas the transmucosal. . .

DRWD . . . for an individualized approach to smoking cessation therapy. Specifically, the total amount of nicotine delivered, the delivery mode, i.e., via **patch** or transmucosal delivery method and regimen, i.e., the order of administration and duration of use of either the **patch** and/or the transmucosal delivery formulation, can be varied to take into account the patient's needs, e.g., the therapeutic indication, the. . .

DRWD For example, according to one embodiment, the transdermal **patch** and transmucosal administration of nicotine are first used concurrently and simultaneously for a period of from about 3 to 12. . . preferably from about 4 to 8 weeks, and most preferably from about 4 to 6 weeks, in which only the **patch** or only the transmucosal nicotine formulation is used.

DRWD Other embodiments will employ different dosage levels of either the **patch** and/or the transmucosal nicotine formulation to suit the needs of those patients with either a relatively high or low nicotine. . . more on the Fagerstrom test, will typically consist of three phases. During the initial phase, a high dosage nicotine transdermal **patch**, typically, with a high loading of nicotine in the range of about 30-60 mg, and preferably, about 40-45 mg, is. . . from about 4 to 8 weeks. Typically, transmucosal administration of nicotine will be used in conjunction with this high dosage **patch**. Subsequently, a transdermal **patch** with a lower loading of nicotine, typically in the range of about 10-30 mg, and preferably, about 20-25 mg, and. . . of from about 4 to 8 weeks. Finally, for a period of from about 4 to 6 weeks, either the **patch** or the transmucosal administration of nicotine may be used alone.

DRWD . . . moderate smoker, i.e., those scoring 6 or less on the Fagerstrom test. For example, during the initial phase, a transdermal **patch** with a moderate loading of nicotine, typically in the range of about 10-40 mg, and preferably, about 25-30 mg, is. . . administration of nicotine. The second phase of this smoking cessation program will consist of administration of a lower dosage transdermal **patch**, typically containing nicotine in the range of about 10-30 mg, and preferably, about 20-25 mg, optionally, with the transmucosal administration. . . used for a period of from about 4 to 8 weeks. During the final phase or weaning period, either the **patch** or transmucosal administration will be used alone.

DRWD . . . cessation program for the light smoker can be developed using the compositions and methods described herein. For example, a transdermal **patch** containing a relatively low loading of nicotine, typically containing nicotine in the range of about 10-30 mg, and preferably, about. . . used for a period of from about 4 to 8 weeks. During the final phase or weaning period, either the **patch** or the transmucosal formulation will be used alone.

DRWD . . . cigarette smoking. Thus, and with many patients, it is possible to reduce the incidence of smoking with either the transdermal **patch** or the transmucosal formulation alone.

DETD TABLE III

Property	Low Dosage **Patch**	High Dosage **Patch**
Dosage Strength	22 mg/20 cm.sup.2	27 mg/20 cm.sup.2
Size (cm.sup.2)	20	20
Nicotine content (mg)	31.4	37.7
24 Hour Delivery (mg).sup.2	22	27
Flux (mg/cm.sup.2 /24 hour).sup.3	1.1	1.35
Total Nicotine Delivered (%)	73	75
Patch Weight (mg)	837	843
Thickness (micron)	333	344

.sup.2 Based on residual content from in vivo performance.

.sup.3 Estimated from in vivo performance.

DETD TABLE IV

Composition	Nicotine **Patch** A	Nicotine **Patch** B
Dosage	22 mg/20 cm.sup.2	27 mg/20 cm.sup.2
Nicotine content (mg)		

31.4 37.7
Acrylic adhesive
70.2 70.2
matrix (mg)
Butylated 0.6 0.6
Hydroxytoluene (mg)
Polyester film
76.0. . .

DETD The **patch**-making procedure and release tests described in Example 9 were repeated using the same membrane, but with a load of 200.

. .

DETD The **patch**-making procedure and release tests described in Example 11 were repeated with a 22- mu m thick film of Sclairfilm HD-2-PA as the membrane. The flux from the **patch** remained roughly constant at about 80 mu g/cm.sup.2 .multidot.h for the first 60 hours, falling to about 30 mu g/cm.sup.2. . .

DETD The **patch**-making procedure and release tests described in Example 11 were repeated with a 50- mu m thick film of Sclairfilm LWS-2-PA as the membrane. The flux from the **patch** remained roughly constant at about 45-50 mu g/cm.sup.2 .multidot.h.

DETD For Example 24, the monolith contained 37 mg of nicotine, with a **patch** area of 5 cm.sup.2. For Example 25, the monolith contained 74 mg of nicotine, with a **patch** area of 10 cm.sup.2. For Example 26, the monolith contained 60 mg of nicotine, with a **patch** area of 20 cm.sup.2. For Example 27, the monolith contained 54 mg of nicotine, with a **patch** area of 30 cm.sup.2.

DETD . . . systems used were manufactured as described in Examples 24-27, and each contained a total of 37 mg nicotine in a **patch** with an area of 5 cm.sup.2, as in Example 24. For Example 28, a single 5 cm.sup.2 transdermal nicotine **patch** was applied to the right forearm of each subject, and the **patch** remained affixed to the forearm for 16 hours. The lowest curve presents the average nicotine plasma level obtained. For Example. . .

DETD . . . state pharmacokinetics of the 22 and 27 mg patches of the present invention with the PROSTEP 22 mg transdermal nicotine **patch**, available from elan pharma, Ltd., Athlone, County Westmeath, Ireland, and manufactured by Lederle Laboratories Division, American Cyanamid Company, Pearl River,. . .

DETD . . . five consecutive days of the treatment period. The resulting blood plasma levels, along with those of the PROSTEP 22 mg **patch** are shown in FIG. 14. The patches of the present invention were well tolerated.

DETD TABLE VI

Transdermal **Patch**.sup.5	Cmax.sup.6 (ng/mL)	Cavg.sup.7 (ng/mL)	Cmin.sup.8 (ng/mL)	Tmax.sup.9 (hrs)
Habitrol .TM. (21 mg/day).sup.10	17 .+-. 2	13 .+-. 2	9 .+-. 2	6 .+-. 3
PROSTEP .TM.				

16 .+-.. . . 11 .+-. 3
4 .+-. 3
(21 mg/day)
NICOTROL .SM.
13.0 .+-. 3.1
8.7 .+-. 2.1
2.5 .+-. 0.8
8 .+-. 3
(15 mg/day)
PATCH OF 16.1 .+-. 7.1
11.2 .+-. 4.1
4.8 .+-. 1.8
8.4 .+-. 1.8
EXAMPLE 1
(22 mg/day)
PATCH OF 23.4 .+-. 8.1
14.5 .+-. 3.3
5.7 .+-. 1.9
8.4 .+-. 3.3
EXAMPLE 2
(27 mg/day)

.sup.5 Competitor product data taken. . .
CLM What is claimed is:
. . . skin-distal side, the depot layer containing a sufficient quantity of
nicotine to maintain a useful flux of nicotine from the **patch** for a total time period of 12 hours or more; (b) an occlusive backing layer in contact with and covering. . .
. . . skin-distal side, the depot layer containing a sufficient quantity of
nicotine to maintain a useful flux of nicotine from the **patch** for a total time period of 12 hours or more; ii. an occlusive backing layer in contact with and covering. . .

L8 ANSWER 7 OF 9 USPATFULL
AN 93:72079 USPATFULL
TI Percutaneously absorbable compositions of morphine or analogous analgesics of morphine
IN Morimoto, Yasunori, 7-22, Nishisakado 4-chome, Sakado-shi, Saitama-ken, 350-02, Japan
Sugibayashi, Kenji, Sakado, Japan
Kobayashi, Kouji, Tokyo, Japan
Kusano, Hisashi, Ageo, Japan
PA Morimoto, Yasunori, Sakado, Japan (non-U.S. individual)
PI US 5240932 19930831
WO 9115241 19911017
AI US 1992-781226 19920107 (7)
WO 1991-JP413 19910329
19920107 PCT 371 date
19920107 PCT 102(e) date
PRAI JP 1991-81180 19910330
DT Utility
FS Granted
EXNAM Primary Examiner: Friedman, S. J.
LREP Spencer, Frank & Schneider
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 15 Drawing Figure(s); 11 Drawing Page(s)
LN.CNT 527

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A composition which is percutaneously absorbable, including a narcotic analgesic selected from the group consisting of morphine and analogous analgesics thereof; from 1 to 20 weight percent of a percutaneous absorption accelerator comprised of one of (a) a terpene and (b) an **essential oil**; from 10 to 60 weight percent of a percutaneous absorption accelerating assistant comprised of one of (a) a lower alcohol having 1-5 carbon atoms, (b) water and (c) a lower glycol having 2-5 carbon atoms.

AB . . . 1 to 20 weight percent of a percutaneous absorption accelerator comprised of one of (a) a terpene and (b) an **essential oil**; from 10 to 60 weight percent of a percutaneous absorption accelerating assistant comprised of one of (a) a lower alcohol. . .

SUMM . . . were used only as injecting agents and oral agents in the past, for percutaneously absorbable type external agents such as **ointment**, cream, tape dressing, plaster dressing, **patch** dressing, and pap dressing (wet dressing), the present inventors have found and attained this invention.

SUMM . . . narcotic or nonnarcotic analgesics into a base agent formed of a percutaneous absorption accelerator consisting of a terpene and/or an **essential oil** and a percutaneous absorption accelerating assistant consisting of a lower alcohol having 1-5 carbon atoms.

SUMM As the percutaneous absorption accelerators, hydrocarbon monoterpenes such as limonene, monoterpene alcohols such as l-**menthol**, terpineol and borneol, monoterpene aldehydes such as citral, monoterpene ketones such as ionone, other monoterpenes such as cineole, or essential. . .

DETD TABLE 1

unit: w %

Sample	This Invention	Comparative Example		
Component	1	1	2	3
Morphine hydrochloride	1	1	1	1
1-**Menthol**	5	--	--	5
Ethanol	40	--	40	--
Water	54	99	59	4

DETD The results showed that the formation having l-**menthol** selected as an absorption accelerator and ethanol as an absorption accelerating assistant has excellent percutaneous absorptivity.

DETD TABLE 3

unit: w %

	This lnvention		
Component	1	2	3
Morphine hydrochloride	1	10	0.01
1-**Menthol**	5	5	5
Ethanol	40	40	40
Water	54	45	54.99

DETD TABLE 5

unit: w %

Component	This Invention 1	4	5
Morphine hydrochloride	1	1	1
1-**Menthol**	5	--	--
Terpineol	--	5	--
Peppermint oil	--	--	5
Ethanol	40	40	40
Water	54	54	54

DETD To examine the effect of the concentration of l-**menthol** on the skin permeability of morphine hydrochloride from an l-**menthol** -ethanol-water system, formations as shown in Table 7 were prepared and examined for percutaneous absorbability.

DETD TABLE 7

unit: w %

Sample	This Invention		Comparative Ex.		
Component	6	1	7	4	5
Morphine hydrochloride	1	1	1	1	1
1-**Menthol**	2.5	5	10	1	0.1
Ethanol	40	40	40	40	40
Water	56.4	54	49	58	58.9

DETD As shown in FIG. 4 and Table 8, the results showed that skin permeativity is excellent when the concentration of **menthol** is 2.5 w % or more.

DETD . . . of the concentration of ethanol, which is a percutaneous absorption accelerating assistant, on skin permeativity of morphine hydrochloride from an l-**menthol**-ethanol-water system, the formulations shown in Table 9 were prepared and examined for percutaneous absorbability.

DETD TABLE 9

unit: w %

Sample	This Invention		Comparative Ex.		
Component	8	1	9	6	7
Morphine hydrochloride	1	1	1	1	1
1-**Menthol**	5	5	5	5	5
Ethanol	20	40	60	80	94
Water	74	54	34	14	--

DETD . . . effect of the concentration of isopropyl alcohol (IPA), employed instead of ethanol, on skin permeativity of morphine hydrochloride from an l-**menthol**-alcohol-water system, the formulations shown in Table 11 were prepared and examined for percutaneous absorbability.

DETD TABLE 11

unit: w %

	This Invention		
Component	10	11	12
Morphine hydrochloride	1	1	1
1-**Menthol**	5	5	5
Ethanol	20	40	60
Water	74	54	34

DETD . . . supplement to ethanol for the percutaneous absorption accelerating assistant having an influence on skin permeativity of morphine hydrochloride from an 1-**menthol**-alcohol-water system, glycerol was mixed as shown in Table 13, and this was comparatively examined for percutaneous absorbability.

DETD TABLE 13

unit: w %		
Sample	This Invention	
Component	1	13
Morphine hydrochloride	1	1
1-**Menthol**	5	5
Ethanol	40	40
Water	54	--
Glycerol	--	54

DETD To examine the skin permeativities of other medicines to an 1-**menthol**-ethanol-water system, formulations using fentanyl citrate (FTC), eptazocine hydrobromide (ETH), cocaine hydrochloride (CCH), and morphine hydrochloride were prepared and examined for. . .

DETD . . . 1 14 15 16

Morphine hydrochloride	1	--	--	--
FTC	--	1	--	--
ETH	--	--	1	--
CCH	--	--	--	1
1-**Menthol**	5	5	5	5
Ethanol	40	40	40	40
Water	54	54	54	54

DETD . . . 8(b) and FIG. 8(c) and Table 16, the results showed that every formulation is excellent in skin permeativity in the 1-**menthol**-ethanol-water system, i.e.,

DETD To examine the effect of different concentration of 1-**menthol** on skin permeativity of eptazocine hydrobromide from an 1-**menthol**-ethanol-water system, formulations as shown in Table 17 were prepared and examined for percutaneous absorbability.

DETD TABLE 17

unit: w %			
Sample	This Invention		
Component	17	18	15
E.T.H.	1	1	1
1-**Menthol**	1	2	5
Ethanol	40	40	40
Water	58	57	54

DETD As shown in FIG. 9 and Table 18, the results showed that skin permeativity is excellent when the concentration of **menthol** is 1.0 wt. % or more.

DETD To examine the effect of the concentration of ethanol on skin permeativity of eptazocine hydrobromide from an l-**menthol** -ethanol-water system, formulations as shown in Table 19 were prepared and examined for percutaneous absorbability.

DETD TABLE 19

unit: w %			
Sample	This Invention		
Component	19	20	15
E.T.H.	1	1	1
l-**Menthol**	5	5	5
Ethanol	10	20	40
Water	84	73	54

DETD To examine the effect of concentration of eptazocine hydrobromide on skin permeativity of eptazocine hydrobromide from an l-**menthol** -ethanol-water system, formulations as shown in Table 21 were prepared and examined for percutaneous absorbability.

DETD TABLE 21

unit: w %			
Sample	This Invention		
Component	21	22	15
E.T.H.	0.1	5	1
l-**Menthol**	5	5	5
Ethanol	40	40	40
Water	54.9	50	54

CLM What is claimed is:

. . . 1 to 20 weight percent of a percutaneous absorption accelerator comprised of one of (a) a terpene and (b) an **essential oil**; from 10 to 60 weight percent of a percutaneous absorption accelerating assistant comprised of one of (a) a lower alcohol. . .

. . . The composition according to claim 1, wherein the percutaneous absorption accelerator is one of (a) a monoterpene and (b) an **essential oil** containing a monoterpene.

. . . 3. The composition according to claim 2, wherein the percutaneous absorption accelerator is a monoterpene and is one of (a) 1-**menthol** and (b) terpineol.

5. The composition according to claim 2, wherein the percutaneous absorption accelerator is an **essential oil** containing a monoterpene and is one of (a) mentha oil and (b) peppermint oil.

IT 64-17-5, Ethanol, biological studies 67-56-1, Methanol, biological studies 67-63-0, Isopropyl alcohol, biological studies 71-23-8, Propanol, biological studies 71-36-3, Butanol, biological studies 71-41-0, Amyl alcohol, biological studies **2216-51-5**, l-Menthol 7732-18-5, Water, biological studies 8000-41-7, Terpineol (absorption promoters contg., for transdermal compns. of analgesics)

L8 ANSWER 8 OF 9 USPATFULL

AN 79:27033 USPATFULL
TI Compositions having a physiological cooling effect
IN Watson, Hugh R., Wargrave, England
Rowsell, David G., Staines, England
Browning, John H. D., Wokingham, England
PA Wilkinson Sword Limited, London, England (non-U.S. corporation)
PI US 4157384 19790605
AI US 1977-837900 19770929 (5)
RLI Division of Ser. No. US 1974-486675, filed on 8 Jul 1974, now abandoned which is a continuation-in-part of Ser. No. US 1972-221753, filed on 28 Jan 1972, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Schenkman, Leonard
LREP Leydig, Voit, Osann, Mayer & Holt, Ltd.
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 812
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Derivatives of p-menthane are disclosed having the property of stimulating the cold receptors of the nervous system of the human body to produce a cold sensation and are used for this purpose in a variety of edible and topical preparations.

SUMM **Menthol** is well known for its physiological cooling effect on the skin and mucous membranes of the mouth and has been extensively used as a flavouring agent (**menthol** being a major constituent of oil of peppermint) in foodstuffs, beverages, dentifrices, mouthwashes, etc. and as a component in a wide range of toiletries, liniments and lotions for topical application. **Menthol** is also a well known tobacco additive for producting a "cool" sensation in the mouth when smoking.

SUMM It is well established that the "cooling" effect of **menthol** is a physiological effect due to the direct action of **menthol** on the nerve endings of the human body responsible for the detection of hot or cold and is not due to latent heat of evaporation. It is believed that the **menthol** acts as a direct stimulus on the cold receptors at the nerve endings which in turn stimulate the central nervous. . .

SUMM Although **menthol** is well established as a physiological coolant its use, in some compositions, is circumscribed by its strong minty odour and. . .

SUMM A few other compounds have been reported in the technical literature as having an odour or flavour similar to **menthol** and from time to time have been proposed as flavourants or odourants in a variety of topical and ingestible compositions.. . . For example, Japanese Patent Publication No. 39-19627 reports that 3-hydroxymethyl p-menthane (menthyl carbinol) has a flavour closely resembling that of 1-**menthol** and suggests its use as a flavourant in confectionery, chewing gum and tobacco. In Swiss Pat. No. 484,032 certain saccharide esters of **menthol** are proposed as additive to tobacco. In French Pat. No. 1,572,332 N,N-Dimethyl 2-ethylbutanamide is reported as having a minty odour. . . odour has also been reported for 2,4,6-trimethylheptan-4-ol and 2,4,6-trimethyl hept-2-en-4-ol in Parfums-Cosmetiques-Savons, May 1956, pp. 17-20. The cooling effect of **menthol** and other related terpene alcohols and their derivatives has also been studied and reported in Koryo, 95, (1970), pp. 39-43.. .

SUMM Despite this knowledge of other compounds having an odour and flavour similar to that of **menthol**, **menthol** is still extensively used in topical, ingestible and other compositions notwithstanding the disadvantages mentioned above, namely its very strong odour. . .

SUMM . . . to provide other compounds having a pronounced physiological cooling effect, in many cases far more persistent than that obtained with **menthol**, without the attendant disadvantages of a strong odour.

DETD . . . methods. Thus, the p-menthane-3-carboxylic acid and its salts may readily be prepared by carbonation of a Grignard reagent derived from **menthol**. The carboxylic acid may then readily be converted into its acid chloride, for example, by reaction with thionyl chloride, and. . .

DETD . . . upon whether the substitution is axially or equatorially into the cis or trans isomer, the four isomers being related as **menthol** is to neomenthol, isomenthol, and neoisomenthol. In general it is found that in the compounds used in this invention the.

.

DETD . . . and for giving an indication of the different relative activities of the compounds, as between themselves and as compared with **menthol**, when applied in a particular manner to a particular part of the body. The results are not necessarily indicative of. . .

DETD . . . for that particular compound. The tests are carried out on a selected panel of 6 people of median sensitivity to 1-**menthol**.

DETD To select a test panel of average sensitivity the following procedure is

used. Known quantities of 1-**menthol** in solution in petroleum ether (bp. 40-60) are placed on 5 mm. squares of filter paper, whereafter the solvent is. . . a time on the tongue and to report on the presence or absence of a cooling effect. The quantity of 1-**menthol** on each impregnated square is gradually reduced from a value substantially above 0.25 .mu.g, the precise range being immaterial. Conveniently, one starts with squares containing 2.0 .mu.g. 1-**menthol**, the amount on each successive square being half that of the preceding square, i.e. the second test square will contain. . . quantity is tested on the tongue at least 10 times. In this way, the thresholds to cold receptor stimulus by 1-**menthol** are determined for each individual of the panel, the threshold for each individual being that amount of 1-**menthol** for which, in a series of not less than 10 test applications, a cooling effect is reported 50% of the time. Six panel members are now selected whose threshold to 1-**menthol** is in the range 0.1 .mu.g to 10 .mu.g and whose average threshold is approximately 0.25 .mu.g., this select panel. . .

DETD . . . according to this invention, the above procedure is repeated using only the 6 selected panel members of average sensitivity to 1-**menthol**. The individual thresholds for each test compound on each of the 6 selected panel members are determined and averaged.

Those.

. .

DETD . . . a natural or synthetic surfactant e.e. a fatty acid salt or a laurylsulphate salt, the composition usually also containing sn **essential oil** or perfume. The range of soap compositions will include soaps of all kinds e.g. toilet soaps, shaving soaps, shaving foams. . .

DETD Antiseptic **Ointment**

DETD An **ointment** was prepared according to the following

formulation:
DETD The final **ointment** when applied to the skin gave rise to a marked cooling effect.
DETD Antipruritic **Ointment**
DETD To the melt was added 0.3% p-menthane-3-carboxamide and the mixture then
allowed to solidify. A soft **ointment** resulted having a soothing effect on the skin accompanied by a noticeable cooling effect.
DETD . . . have shown that the compounds are substantially non toxic. LD values for mice are in excess of 2 g/kg. Enclosed **patch** tests on the skin have shown an extremely low level of allergic response even in persons known to be extremely. . .

L8 ANSWER 9 OF 9 USPATFULL
AN 79:4484 USPATFULL
TI P-Menthane carboxamides having a physiological cooling effect
IN Watson, Hugh R., Wargrave, England
Rowsell, David G., Staines, England
Spring, David J., Datchet, England
PA Wilkinson Sword Limited, London, United Kingdom (non-U.S. corporation)
PI US 4136163 19790123
AI US 1974-486564 19740708 (5)
RLI Continuation-in-part of Ser. No. US 1972-221755, filed on 28 Jan 1972, now abandoned
PRAI GB 1971-3928 19710204
GB 1971-3934 19710204
DT Utility
FS Granted
EXNAM Primary Examiner: Schenkman, Leonard
LREP Leydig, Voit, Osann, Mayer & Holt, Ltd.
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 841
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB N-substituted-p-menthane-3-carboxamides are disclosed having the property of stimulating the cold receptors of the nervous system of the human body to produce a cold sensation and are used for this purpose in a variety of edible and topical preparations.
SUMM **Menthol** is well known for its physiological cooling effect on the skin and mucous membranes of the mouth and has been extensively used
as a flavouring agent (**menthol** being a major constituent of oil of peppermint) in foodstuffs, beverages, dentifrices, mouthwashes, etc. and as a component in a wide range of toiletries, liniments and lotions for topical application. **Menthol** is also a well known tobacco additive for producing a "cool" sensation in the mouth when smoking.
SUMM It is well established that the "cooling" effect of **menthol** is a physiological effect due to the direct action of **menthol** on the nerve endings of the human body responsive for the detection of hot or cold and is not due to latent heat of evaporation. It is believed that the **menthol** acts as a direct stimulus on the cold receptors at the nerve endings which in turn stimulate the central nervous. . .
SUMM Although **menthol** is well established as a physiological coolant its use, in some compositions, is circumscribed by its strong minty odour and. . .
SUMM A few other compounds have been reported in the technical literature as having an odour or flavour similar to **menthol** and from time to

time have been proposed as flavourants or odourants in a variety of topical and ingestible compositions.. . . For example, Japanese Patent Publication No. 39-19627 reports that 3-hydroxymethyl p-menthane (menthyl carbinol) has a flavour closely resembling that of 1-**menthol** and suggests its use as a flavourant; in confectionery, chewing gum and tobacco. In Swiss Patent No. 484,032 certain saccharide esters of **menthol** are proposed as additive to tobacco. In French Pat. Spec. No. 1,572,332 N,N-Dimethyl 2-ethylbutanamide is reported as having a minty. . . odour has also been reported for 2,4,6-trimethylheptan-4-ol and 2,4,6-trimethyl hept-2-en-4-ol in Parfums-Cosmetiques-Savons, May 1956, pp. 17-20. The cooling effect of **menthol** and other related terpene alcohols and their derivatives has also been studied and reported in Koryo, 95, (1970), pp. 39-43.. . .

SUMM Despite this knowledge of other compounds having an odour and flavour similar to that of **menthol**, **menthol** is still extensively used in topical, ingestible and other compositions notwithstanding the disadvantages mentioned above, namely its very strong odour. . .

SUMM . . . to provide other compounds having a pronounced physiological cooling effect, in many cases far more persistent than that obtained with **menthol**, without the attendant disadvantages of a strong odour.

DETD . . . upon whether the substitution is axially or equatorially into the cis or trans isomer, the four isomers being related as **menthol** is to neomenthol, isomenthol, and neoisomenthol. In general it is found that in the compounds used in this invention the. . .

DETD . . . and for giving an indication of the different relative activities of the compounds, as between themselves and as compared with **menthol**, when applied in a particular manner to a particular part of the body. The results are not necessarily indicative of. . .

DETD . . . for that particular compound. The tests are carried out on a selected panel of 6 people of median sensitivity to 1-**menthol**.

DETD To select a test panel of average sensitivity the following procedure is used. Known quantities of 1-**menthol** in solution in petroleum ether (bp.40-60) are placed on 5 mm. squares of filter paper, whereafter the solvent is allowed. . . a time on the tongue and to report on the presence or absence of a cooling effect. The quantity of 1-**menthol** on each impregnated square is gradually reduced from a value substantially above 0.25 .mu.g. per square to substantially below 0.25 .mu.g, the precise range being immaterial. Conveniently, one starts with squares containing 2.0 .mu.g. 1-**menthol**, the amount on each successive square being half that of the preceding square, i.e. the second test square will contain. . . quantity is tested on the tongue at least 10 times. In this way, the thresholds to cold receptor stimulus by 1-**menthol** are determined for each individual of the panel, the threshold for each individual being that amount of 1-**menthol** for which, in a series of not less than 10 test applications, a cooling effect is reported 50% of the time. Six panel members are now selected whose threshold to 1-**menthol** is in the range 0.1 .mu.g to 10 .mu.g and whose average threshold is approximately 0.25 .mu.g., this select panel. . .

DETD . . . according to this invention, the above procedure is repeated using only the 6 selected panel members of average sensitivity to 1-

menthol. The individual thresholds for each test compound on each of the 6 selected panel members are determined and averaged. Those.

. .

DETD . . . a natural or synthetic surfactant e.e. a fatty acid salt or a lauryl sulphate salt, the composition usually, containing an **essential oil** or perfume. The range of soap compositions will include soaps of all kinds e.g. toilet soaps, shaving soaps, shaving foams. . .

DETD Antiseptic **Ointment**

DETD An **ointment** was prepared according to the following formulation:

DETD The final **ointment** when applied to the skin gave rise to a marked cooling effect.

DETD Antipruritic **Ointment**

DETD To the melt was added 0.1% of N-(p-menth-3-oyl)glycine n-propyl ester and the mixture was then allowed to solidify. A soft **ointment** resulted having a soothing effect on the skin accompanied by a noticeable cooling effect.

DETD . . . this invention have shown that the compounds are substantially non toxic, LD.sub.50 levels in mice being higher than 2g/kg. Enclosed **patch** tests on the skin, on both rabbits and humans, have shown an extremely low level of allergic response even in. . .